

# Pd-C induced Catalytic Transfer Hydrogenation with Triethylsilane

Pijus K. Mandal and John S. McMurray

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**Numbering Scheme:** Compounds are numbered according to Table 1 of the paper. For example, compound **1a** is the substrate for the hydrogenation reaction of entry 1 and compound **1b** is the product.

## General Methods

Compounds were tested for purity by thin layer chromatography (silica gel) using mixtures of EtOAc in hexanes as the eluant. Fmoc-amino acid were tested for purity using reverse phase HPLC on a 4.6 x 250 mm C18 column using a gradient of 10% - 50% ACN/30 min (A) or 10% - 80% ACN/30 min (B) at 1.5 ml/min. Both H<sub>2</sub>O and ACN contained 0.1% TFA. Elution was monitored at 230 and 275 nM. NMR spectra were acquired on a 300 MHz spectrometer. Chemical shifts are referenced to TMS, 0.0 ppm. Proton NMR signals were characterized by chemical shift value, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constant in Hz, and the number of protons obtained by integration of the spectra. Carbon spectra were characterized by chemical shift value relative to TMS (0.0 ppm). Dry solvents were obtained commercially. New compounds were characterized by HRMS, proton NMR, and carbon NMR.

*Preparation of diethyl allylmethylmalonate (**1a**)*. Prepared as in ref. 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25 (t, *J* = 7.2 Hz, 6H), 1.4 (s, 3H), 2.61 (d, *J* = 7.5Hz, 2H), 4.18 (q, *J* = 7.2Hz, 4H), 5.07-5.13 (m, 2H), 5.63-5.72 (m, 1H).

*Diethyl methyl propylmalonate (**1b**, **2b**)*. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.93 (t, *J* = 7.2Hz, 3H), 1.2-1.3 (overlap, 8H), 1.4 (s, 3H), 1.8-1.86 (m, 2H), 4.16 (q, *J* = 7.2Hz, 4H). HRMS (M+H) calcd. for C<sub>11</sub>H<sub>21</sub>O<sub>4</sub>: 217.1440; found 217.1440. Compound **1b/2b** was reported but not well characterized in the literature, e.g. reference 2. Therefore we reported <sup>1</sup>H NMR and HRMS data

*Preparation of diethyl methylpropargylmalonate (**2a**)*. Prepared as described in ref. 3, using propargyl bromide as the electrophile. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25 (t, *J* = 7.2Hz, 6H), 1.55 (s, 3H), 2.02 (m, 1H), 2.78 (d, *J* = 2.4 Hz, 2H), 4.20 (q, *J* = 7.4 Hz).

*Preparation of 4(S)-[(9-fluorenylmethoxycarbonyl)amino]-2-pentenoic acid benzyl ester (**3a**)*: A solution of Fmoc-Alaninal<sup>4</sup> (1g, 3.4 mmol) and benzyl (triphenylphosphoranylidene)acetate (1.5g, 3.75mmol) in 15 mL of dry CH<sub>2</sub>Cl<sub>2</sub> was stirred for 4h. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography, eluting with 15% EtOAc-hexane. Yield 1.4g (95%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.28 (d, *J* = 6.6 Hz, 3H), 4.2 (t, *J* = 6.6 Hz, 1H), 4.3-4.4 (m, 3H), 4.71 (d, *J* = 8.7 Hz, 1H), 5.93 (d, *J* = 15.9 Hz, 1H), 6.91 (dd, *J* = 3.9, 15.6 Hz, 1H), 7.25-7.4 (m, 9H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H). HRMS (M+H) calcd. for C<sub>27</sub>H<sub>26</sub>NO<sub>4</sub>: 428.1862; found 428.1862.

*N-(9-Fluorenylmethoxycarbonyl)-4-methyl-4-aminobutyric acid (**3b**)*: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.24 (d, *J* = 6.6 Hz, 2H), 1.62 (m, 2H), 2.2 (m, 2H), 3.51 (m, 1H), 4.18-4.35 (m, 3H), 7.15 (d, *J* = 6.6 Hz, 1H), 7.3-7.43 (m, 4H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.88 (d, *J* = 7.2 Hz, 2H). HRMS (M+H) calcd. for C<sub>20</sub>H<sub>22</sub>NO<sub>4</sub>: 340.1549; found 340.1556.

*Preparation of tert-butyl 4-hydroxycinnamate (**4a**)*. Prepared as described in reference 5. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.54 (s, 9H), 6.22 (d, *J* = 15.9 Hz, 1H), 6.64 (brs, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 15.9 Hz, 1H).

*t*-Butyl-3-(4-hydroxyphenyl)propionate (**4b**). Identical to product **7i** in reference 6.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.42 (s, 9H), 2.50 (t,  $J = 7.2$  Hz, 2H), 2.83 (t,  $J = 7.2$  Hz, 2H), 6.72 (d,  $J = 8.4$  Hz, 2H), 7.02 (d,  $J = 8.7$  Hz, 2H).

*Preparation of methyl-4N(9-fluorenylmethylcarbonyl)amino, but-2-ynoate (**5a**)* Methyl-4,N(*tert*-butoxycarbonyl)amino-but-2-ynoate<sup>7</sup> was treated with TFA for 30 min and the acid evaporated *in vacuo*. Fmoc-OSu was added in the presence of 4 eq. of  $\text{Na}_2\text{CO}_3$  in dioxane/water 1:1. On completion of the reaction (TLC) the solution was washed with EtOAc, acidified with conc HCl to pH 2.0, then extracted with EtOAc. The solvent was evaporated off *in vacuo* and the solid product obtained by trituration with  $\text{Et}_2\text{O}$  and hexane.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.77 (s, 3H), 4.11-4.16 (m, 2H), 4.20-4.23 (m, 1H), 4.43 (d,  $J = 6.9$  Hz, 2H), 5.25 (brs, 1H), 7.25-7.49 (m, 4H), 7.58 (d,  $J = 7.5$  Hz, 2H), 7.76 (d,  $J = 7.5$  Hz, 2H). HRMS (M+H) calcd. for  $\text{C}_{20}\text{H}_{18}\text{NO}_4$ : 336.1236; found : 336.1239.

*Methyl-4,N(9-fluorenylmethylcarbonyl)amino, butanoate (**5b**)*. Identical to compound **12** in reference 8.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.85 (m, 2H), 2.36 (m, 2H), 3.25 (m, 2H), 3.7 (s, 3H), 4.18-4.23 (m, 1H), 4.40 (d,  $J = 6.6$  Hz, 2H), 4.9 (brs, 1H), 7.28-7.42 (m, 4H), 7.58 (d,  $J = 7.5$  Hz, 2H), 7.75 (d,  $J = 7.5$  Hz, 2H). HRMS (M+H) calcd. for  $\text{C}_{20}\text{H}_{22}\text{NO}_4$ : 340.1549; found : 340.1549.

*Preparation of methyl 5-phenyl-2,4-pentadienoate (**6a**)*. A solution of methyl (triphenylphosphoranylidene) acetate (2.8 g, 8.32 mmol) and cinnamaldehyde (1g, 7.56 mmol) in 20 mL of dry  $\text{CH}_2\text{Cl}_2$  was stirred overnight. Solvent was removed *in vacuo*, crude obtained then purified by silica gel column chromatography, eluting with 10% EtOAc-hexane. Yield 1.3g (92%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.76 (s, 3H), 5.98 (d,  $J = 15.5$  Hz, 1H), 6.8-6.93 (m, 2H), 7.25-7.38 (m, 3H), 7.40-7.50 (m, 3H). Identical to compound (E,E)-7 in reference 9.

*Methyl 5-phenyl-pentanoate (**6b**)*. Identical to compound **3a** in reference 10.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.62-1.76 (m, 4H), 2.34-2.38 (m, 2H), 2.63-2.68 (m, 2H), 3.68 (s, 3H), 7.18-7.22 (m, 3H), 7.28-7.32 (m, 2H).

*Preparation of 1-hydroxy-1-(3,5-dimethoxyphenyl)-2-butene (**7a**)*. To a stirred solution of 3,5 dimethoxybenzaldehyde (1 g, 6.02 mmol) in dry THF (20 mL), at 0°C, a solution of propenylmagnesium bromide (15 mL) in THF was added dropwise. The reaction was stirred overnight, quenched with 10%  $\text{NH}_4\text{Cl}$  (aq) and extracted with ether (3 × 30mL). Organic part was washed with water (2 × 20 mL) followed by brine and dried ( $\text{MgSO}_4$ ). The solution was evaporated to dryness and the product was purified by silica gel column chromatography eluting with 30% EtOAc-hexane. Yield 1.2g, (95%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.72 (d,  $J = 6.0$  Hz, 2H, minor isomer), 1.78 (d,  $J = 6.0$  Hz, 2H, major isomer), 3.8 (s, 6H), 5.07 (d,  $J = 6$  Hz, 1H, minor isomer), 5.5 (d,  $J = 6.0$  Hz, 2H, major isomer), 5.58-5.80 (m, 2H), 6.37 (m, 1H), 6.54-6.57 (m, 2H). HRMS (M+H) calcd. for  $\text{C}_{12}\text{H}_{17}\text{O}_3$ : 209.1178; found 209.1180. Compound **7a** was reported but not well characterized in the literature, e.g. reference 11. Therefore we reported  $^1\text{H}$  NMR and HRMS data.

*1-(3,5-dimethoxyphenyl)-butane (**7b**)*.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.93 (t,  $J = 7.8$  Hz, 3H), 1.29-1.43 (m, 2H), 1.53-1.64 (m, 2H), 2.55 (t,  $J = 7.8$  Hz, 2H), 3.8 (s, 6H), 6.3 (m, 1H), 6.35 (m, 2H). HRMS (M+H) calcd. for  $\text{C}_{12}\text{H}_{19}\text{O}_2$ : 195.1385; found 195.1388. Compound **7b** was reported but not well characterized in the literature, e.g. reference 12. Therefore we reported  $^1\text{H}$  NMR and HRMS data.

*Preparation of 1-hydroxy-1-(3,5-dimethoxyphenyl)-propyne (**8a**)*. The same procedure as in described for **7a** was used with propynylmagnesium bromide in place of propenylmagnesium bromide. Yield 1.1g, (96%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.65 (s, 1H), 3.78 (s, 6H), 5.37 (m, 1H), 6.41 (m, 1H), 6.7 (m, 2H). HRMS (M+H) calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_3$ : 193.0865; found: 193.0869.

*1-(3,5-dimethoxyphenyl)-propane (**8b**)*.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.94 (t,  $J = 7.2$  Hz, 3H), 1.63 (m, 2H), 2.55 (t,  $J = 7.5$  Hz, 2H), 3.78 (s, 6H), 6.32 (m, 1H), 6.37 (m, 2H). Reported in reference 13.

*Preparation of Fmoc-Leu-OBn (**9a**)*. To a stirred solution of Fmoc-Leu-OH (1g, 2.83 mmol) and DIEA (1.08 mL, 6.22 mmol) in 10 ml of dry THF at 0°C, benzyl bromide (0.435g, 2.54 mmol) in 2mL dry THF was added under  $\text{N}_2$  and the mixture stirred for 6h. The solvent was removed and the residue was taken up in 50 mL of EtOAc. The organic layer was then washed with 5% HCl (2 × 15mL), 10%  $\text{NaHCO}_3$  (1 × 20mL) and brine (1 × 15mL). It was dried ( $\text{MgSO}_4$ ) and solvent was evaporated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with 25% EtOAc-hexane. Yield 1.2g (92%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.92 (m, 6H), 1.5-1.67 (m, 3H), 4.20 (m, 1H), 4.38-4.48 (m, 3H), 5.16 (m, 3H), 7.27-7.41 (m, 9H), 7.58 (d,  $J = 7.5$  Hz, 2H), 7.75 (d,  $J = 7.5$  Hz, 2H). Identical to compound **3g** in reference 14.

*Fmoc-Leu-OH (**9b**)*.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88-0.99 (m, 6H), 1.56-1.75 (m, 3H), 4.24 (t,  $J = 6.9$  Hz, 1H), 4.44-4.5 (m, 2H), 5.14 (d,  $J = 8.1$  Hz, 1H), 7.28-7.44 (m, 4H), 7.6 (m, 2H), 7.8 (d,  $J = 7.5$  Hz, 2H).

*H-Tyr-OMe (**10b**)*.  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  2.95-3.09 (m, 2H), 3.66 (s, 3H), 4.13 (q,  $J = 6.3$  Hz, 1H), 6.72 (d,  $J = 8.4$  Hz, 2H), 7.00 (d,  $J = 8.4$  Hz, 2H), 8.6 (m, 3H), 9.45 (brs, 1H). Identical to commercial material.

*Transprotection of Z-Val-OMe to Boc-Val-OMe (**11b**)*.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.9 (d,  $J = 6.9$  Hz, 3H), 0.96 (d,  $J = 6.9$  Hz, 3H), 1.45 (s, 9H), 2.13 (m, 1H), 3.75 (s, 3H), 4.22 (m, 1H), 5.03 (brs, 1H). Identical to commercial material.

*Preparation of Boc-Ser(OBzl)-OMe (**12a**)*. A mixture of Boc-Ser(OBzl)-OH (1 g, 3.38 mmol), DCC (0.7 g, 3.38 mmol) and DMAP (0.04 g, 0.33 mmol) in dry methanol (25 mL) were stirred overnight. After filtration (celite) the filtrate was concentrated under vacuum. It was diluted with 100 mL of ether and the organic layer was washed with 5% HCl (1 × 20mL), 10%  $\text{NaHCO}_3$  solution (2 × 20ml), dried ( $\text{MgSO}_4$ ) and the solvent evaporated. The crude product was purified by silica gel column chromatography, eluting with 25% EtOAc-hexane. Yield 0.9 g (88%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.51 (s, 9H), 3.7 (dd,  $J = 3.3, 9.3$  Hz, 1H), 3.75 (s, 3H), 3.88 (dd,  $J = 3.0, 9.3$  Hz, 1H), 4.46 (m, 1H), 4.5 (d,  $J = 20.1$  Hz, 1H), 4.55 (d,  $J = 20.1$  Hz, 1H), 5.41 (d,  $J = 8.1$  Hz, 1H), 7.27-7.38 (m, 5 H). Identical to compound **3h** in reference 15.

*Boc-Ser-OMe (**12b**)*.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.46 (s, 9H), 3.79 (s, 3H), 3.88 (m, 2H), 4.38 (m, 1H), 5.51 (brs, 1H). Identical to commercial material.

*Preparation of Boc-Thr(OBzl)-OMe (**13a**)*. Followed as same procedure as described for **12a**, using Boc-Thr(OBzl)-OH, DCC, DMAP (cat.) in methanol.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27 (d,  $J = 6.3$

Hz, 3H), 1.47 (s, 9H), 3.68 (s, 3H), 4.12 (m, 1H), 4.32 (dd,  $J$  = 2.1, 9.4 Hz, 1H), 4.38 (d,  $J$  = 12.0 Hz, 1H), 4.57 (d,  $J$  = 12.0 Hz), 5.28 (d, 8.2 Hz, 1H), 7.25-7.38 (m, 5H).

*Boc-Thr-OMe (13b).*  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25 (d,  $J$  = 6.3 Hz, 3H), 1.45 (s, 9H), 3.77 (s, 3H), 4.24-4.3 (m, 2H), 5.39 (brs, 1H). Identical to commercial material.

*Preparation of 1-(4-methoxyphenyl)-3-isopropyl-4(4-benzyloxyphenyl)-azetidine-2-one 14a.* A solution of *N*-(4-benzyloxybenzylidene)-*p*-anisidine (1 g, 3.15 mmol), isovaleryl chloride (0.46 mL, 3.78 mmol) and tributylamine (1.5 mL, 6.3 mmol) in 15mL of dry toluene was heated at reflux for 6h. After cooling to room temperature the mixture was diluted with additional 20 mL of toluene. The organic layer was washed with 5% HCl (3  $\times$  15 mL) followed by 10%  $\text{NaHCO}_3$  (1  $\times$  20mL) and brine. It was dried ( $\text{MgSO}_4$ ) and solvent was evaporated *in vacuo*. The crude product was purified by silica gel chromatography eluting with 20% EtOAc-hexane. Yield 0.95 g (75%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.06 (d,  $J$  = 6.6 Hz, 3H), 1.13 (d,  $J$  6.6 Hz, 3H), 2.16 (m, 1H), 2.86 (dd,  $J$  = 2.1, 8.1 Hz, 1H), 3.73 (s, 3H), 4.63 (d,  $J$  = 2.1 Hz, 1H), 5.04 (s, 2H), 6.74-6.79 (m, 2H), 6.94-6.98 (m, 2H), 7.19-7.27 (m, 4H), 7.32-7.43 (m, 5H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.2, 20.4, 28.7, 55.4, 58.8, 67.2, 70.1, 114.3, 115.4, 118.2, 127.2, 127.5, 128.1, 128.6, 130.6, 131.4, 136.8, 155.8, 158.8, 166.9. HRMS (M+H) calcd. for  $\text{C}_{26}\text{H}_{28}\text{NO}_3$ : 402.2069; found 402.2065.

*1-(4-methoxyphenyl)-3-isopropyl-4(4-hydroxyphenyl)-azetidine-2-one 14b.*  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  0.96 (d,  $J$  = 6.6 Hz, 3H), 1.02 (d,  $J$  = 6.6 Hz, 3H), 2.05 (m, 1H), 2.78 (dd,  $J$  = 2.4, 8.4 Hz, 1H), 3.64 (s, 3H), 4.79 (d,  $J$  = 2.1Hz, 1H), 6.70-6.73 (m, 2H), 6.8-6.84 (m, 2H), 7.11-7.18 (m, 4H), 9.41 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  20.3, 20.6, 28.6, 55.6, 58.2, 66.7, 114.7, 116.1, 118.4, 127.9, 131.4, 155.7, 157.6, 157.7. HRMS (M+H) calcd. for  $\text{C}_{19}\text{H}_{22}\text{NO}_3$ : 312.1600; found 312.1600

*Preparation of Fmoc-L-aspartic acid  $\beta$ -methyl ester  $\alpha$ -allyl ester (15a).* A mixture of Fmoc-Asp(OH)-OAll (0.5 g, 1.26 mmol), EDCI (0.3 g, 1.56 mmol) and DMAP (0.016 g, 0.13 mmol) in dry methanol (10 mL) was stirred overnight. The solvent was removed and the product was diluted with 100 mL of EtOAc. The organic layer was washed with 5% conc HCl (1  $\times$  20mL), 10%  $\text{NaHCO}_3$  (2  $\times$  20ml) and dried over  $\text{MgSO}_4$ . The product was pure enough for the next step. Yield 0.890 g (86%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.87 (dd,  $J$  = 4.5, 17.1 Hz, 1H), 3.06 (dd,  $J$  = 4.5, 17.1 Hz, 1H), 3.69 (s, 3H), 4.22 (t,  $J$  = 6.9 Hz, 1H), 4.32-4.46 (m, 2H), 4.6-4.7 (m, 3H), 5.25 (dd,  $J$  = 1.2, 10.5 Hz, 1H), 5.33 (dd,  $J$  = 1.2, 17.1 Hz, 1H), 5.81-5.92 (m, 2H), 7.27-7.41 (m, 4H), 7.58 (d,  $J$  = 7.2 Hz, 2H), 7.74 (d,  $J$  = 7.5 Hz, 1H). HRMS (M+H) calcd. for  $\text{C}_{23}\text{H}_{24}\text{NO}_6$ : 410.1604; found 410.1603.

*Fmoc-Asp(OMe)-OH (15b).*  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  2.75 (m, 2H), 3.61 (s, 3H), 4.20-4.42 (m, 4H), 7.30-7.44 (m, 4H), 7.7 (m, 3H), 7.89 (d,  $J$  = 7.5 Hz, 2H), 12.87 (brs, 1H). Identical to commercial material.

*Preparation of Boc-L-aspartic acid  $\beta$ -benzyl ester  $\alpha$ -propargyl ester (16a).* To a stirred solution of Boc-Asp(OBzl)-OH (1 g, 3.1 mmol) and DIEA (1.6 mL, 9.3 mmol) in 20 mL of dry  $\text{CH}_2\text{Cl}_2$  at 0°C, propargyl bromide (1 g, 6.2 mmol) in 2 mL dry  $\text{CH}_2\text{Cl}_2$  was added dropwise under  $\text{N}_2$ . Stirring was continued overnight at rt. The mixture was diluted with 50 mL of  $\text{CH}_2\text{Cl}_2$  and the solution was washed with 5% conc. HCl (2  $\times$  15 mL), 10%  $\text{NaHCO}_3$  (1  $\times$  20 mL), brine and dried over  $\text{MgSO}_4$ . The solvent was evaporated *in vacuo*. The crude product was pure enough for the next step. Yield 0.78g (70%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.44 (s, 9H), 2.45 (t,  $J$  = 2.4 Hz, 1H),

2.88 (dd,  $J$  = 4.8, 17.1 Hz, 1H), 3.06 (dd,  $J$  = 4.5, 16.8 Hz, 1H), 4.62 (m, 1H), 4.68 (m, 2H), 5.13 (s, 2H), 5.46 (d,  $J$  = 8.4 Hz, 1H), 7.29-7.39 (m, 5H). HRMS (M+H) calcd. for C<sub>19</sub>H<sub>24</sub>NO<sub>6</sub>: 362.1604; found 362.1600.

**16b.** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.89 (t,  $J$  = 7.5 Hz, 3H), 1.41 (s, 9H), 1.61 (m, 2H), 2.82 (d,  $J$  = 17.1 Hz, 1H), 3.01 (d,  $J$  = 16.8 Hz, 1H), 4.08 (t,  $J$  = 6.9 Hz, 2H), 4.54 (m, 1H), 5.54 (d, 8.4 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 10.2, 21.8, 28.3, 36.5, 49.8, 67.4, 80.3, 155.6, 171.0, 175.7. HRMS (M+H) calcd. for C<sub>12</sub>H<sub>22</sub>NO<sub>6</sub>: 276.1447; found 276.1448.

*Preparation of Alloc-Leu-OMe (17a, 18a).* To a stirred suspension of H-Leu-OMe·HCl (1 g, 5.5 mmol) and allylchloroformate (0.9 mL, 8.3 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0°C, DIEA (2.8 mL, 16.5 mmol) was added dropwise under N<sub>2</sub>. Stirring was continued for 4 h. The reaction mixture was diluted with an additional 50ml of CH<sub>2</sub>Cl<sub>2</sub>. The solution was washed with 5% conc HCl (3 × 20 mL) followed by brine (1 × 20mL) and dried over MgSO<sub>4</sub>. The solvent was removed under vacuum. The crude product was purified by silica gel column chromatography eluting with 20% EtOAc-hexane. Yield 1.2 g (95%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.94 (m, 6H), 1.48-1.76 (m, 3H), 3.74 (s, 3H), 4.39 (m, 1H), 4.57 (d,  $J$  = 5.4 Hz, 2H), 5.21 (d,  $J$  = 10.5 Hz, 1H), 5.30 (d,  $J$  = 17.1 Hz, 1H), 5.92 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.6, 22.7, 24.6, 41.5, 52.1, 52.4, 65.7, 117.6, 132.6, 155.8, 173.7. HRMS (M+H) calcd. for C<sub>11</sub>H<sub>20</sub>NO<sub>4</sub>: 230.1392; found 230.1396. Compound **17a/18a** was reported but not well characterized in the literature, e.g. reference 16. Therefore we reported <sup>1</sup>H NMR and HRMS data

*H-Leu-OMe (17b).* <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.00 (d,  $J$  = 6.0 Hz, 6H), 1.84-2.02 (m, 3H), 3.83 (s, 3H), 4.09 (m, 1H), 8.8 (br, 2H). Identical to commercial starting material for **17a**.

*Transprotection of Alloc-Leu-OMe (17a) to Boc-Leu-OMe (18b).* <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.93-0.98 (m, 6H), 1.44 (s, 9H), 1.48-1.74 (m, 3H), 3.73 (s, 3H), 4.31 (m, 1H), 4.9 (brs, 1H). HRMS (M+H) calcd. for C<sub>12</sub>H<sub>24</sub>NO<sub>4</sub>: 246.1705; found 246.1707.

*Methyl 3,4-dinitrobenzoate (19a)* was obtained commercially

*Methyl 3,4-diaminobenzoate (19b)*<sup>17</sup> <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 3.76 (s, 3H), 6.01 (br, 4H), 6.21 (s, 1H), 6.6 (s, 2H).. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ 52.2, 106.1, 106.2, 131.2, 148.0, 167.4. HRMS (M+H) calcd. for C<sub>8</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>: 167.0821; found 167.0822.

*Methyl 4-nitrobutyrate (20a)* was obtained commercially

*Methyl 4-amino-butyrate (20b).* <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.14 (m, 2H), 2.53 (t,  $J$  = 6.9 Hz, 2H), 3.16 (t,  $J$  = 7.5 Hz, 1H), 3.39 (t,  $J$  = 7.2 Hz, 1H), 3.68 (s, 3H), 7.88 (brs, 3H). Identical to commercially available compound.

*Preparation of 1-azido-2-(9-fluorenylmethoxycarbonylamino)-propane (21a).* Followed as same procedure as in reference 18, starting from Fmoc-Alanolinol.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.24 (d,  $J$  = 9.6 Hz, 3H), 3.38 (m, 2H), 3.93 (m, 1H), 4.21 (t,  $J$  = 9.6 Hz, 1H), 4.43 (m, 2H), 4.77 (brs, 1H), 7.29-7.42 (m, 4H), 7.58 (d,  $J$  = 7.5 Hz, 2H), 7.77 (d,  $J$  = 7.5 Hz, 2H). Identical to compound **3a** in reference 19.

*1-amino-2-(9-fluorenylmethoxycarbonylamino)-propane hydrochloride (21b).*  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>)  $\delta$  1.1 (d,  $J = 6.6$  Hz, 3H), 2.8 (brs, 2H), 3.76 (m, 1H), 4.22-4.4 (m, 3H), 7.31-7.44 (m, 4H), 7.71 (d,  $J = 7.8$  Hz, 2H), 7.89 (d,  $J = 7.5$  Hz, 2H), 8.04 (br 3H). HRMS (M+H) calcd. for C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>: 297.1606; found 297.1603. Compound **21b** was reported but not well characterized reference 20. Therefore we reported  $^1\text{H}$  NMR and HRMS data.

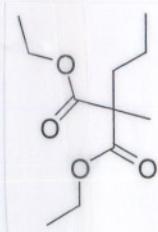
*Preparation of N-benzylidine leucine methyl ester (22a).* Prepared as described in reference 21.  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  0.89 (d,  $J = 6.6$  Hz, 3H), 0.94 (d,  $J = 6.6$  Hz, 3H), 1.57 (m, 1H), 1.84 (m, 2H), 3.73 (s, 3H), 4.08 (dd,  $J = 9.6$  Hz, 1H), 7.4-7.43 (m, 3H), 7.76-7.79 (m, 2H), 8.28 (s, 1H).

*N-benzyl leucine methyl ester (22b).* Identical to compound **1** in reference 22.  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  0.84 (d,  $J = 6.6$  Hz, 3H), 0.91 (d,  $J = 6.6$  Hz, 3H), 1.45 (m, 2H), 1.71-1.84 (m, 2H), 3.33 (t,  $J = 7.2$  Hz, 1H), 3.63 (d,  $J = 12.9$  Hz, 1H), 3.73 (s, 3H), 3.83 (d,  $J = 12.9$  Hz), 7.23-7.36 (m, 5H).

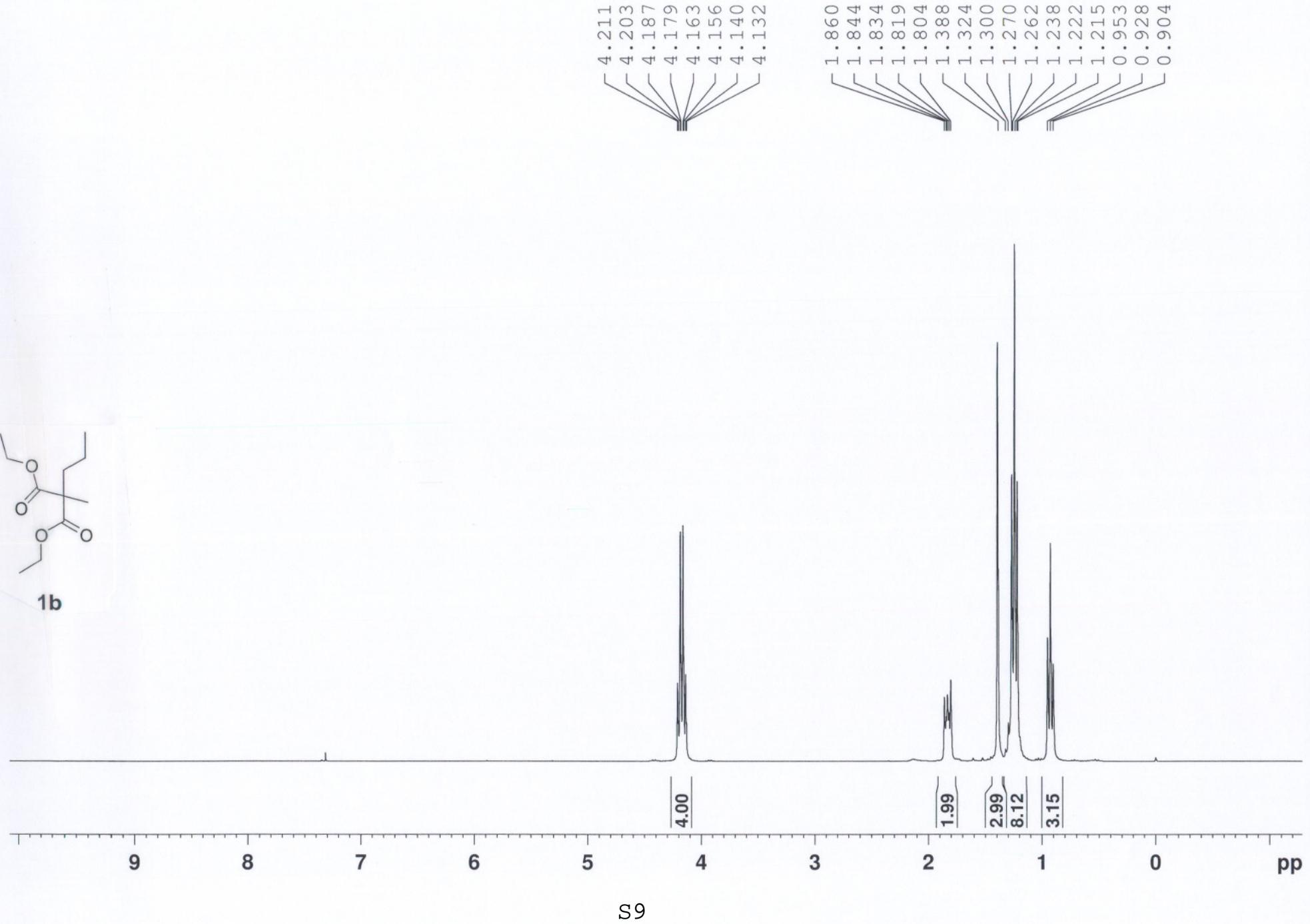
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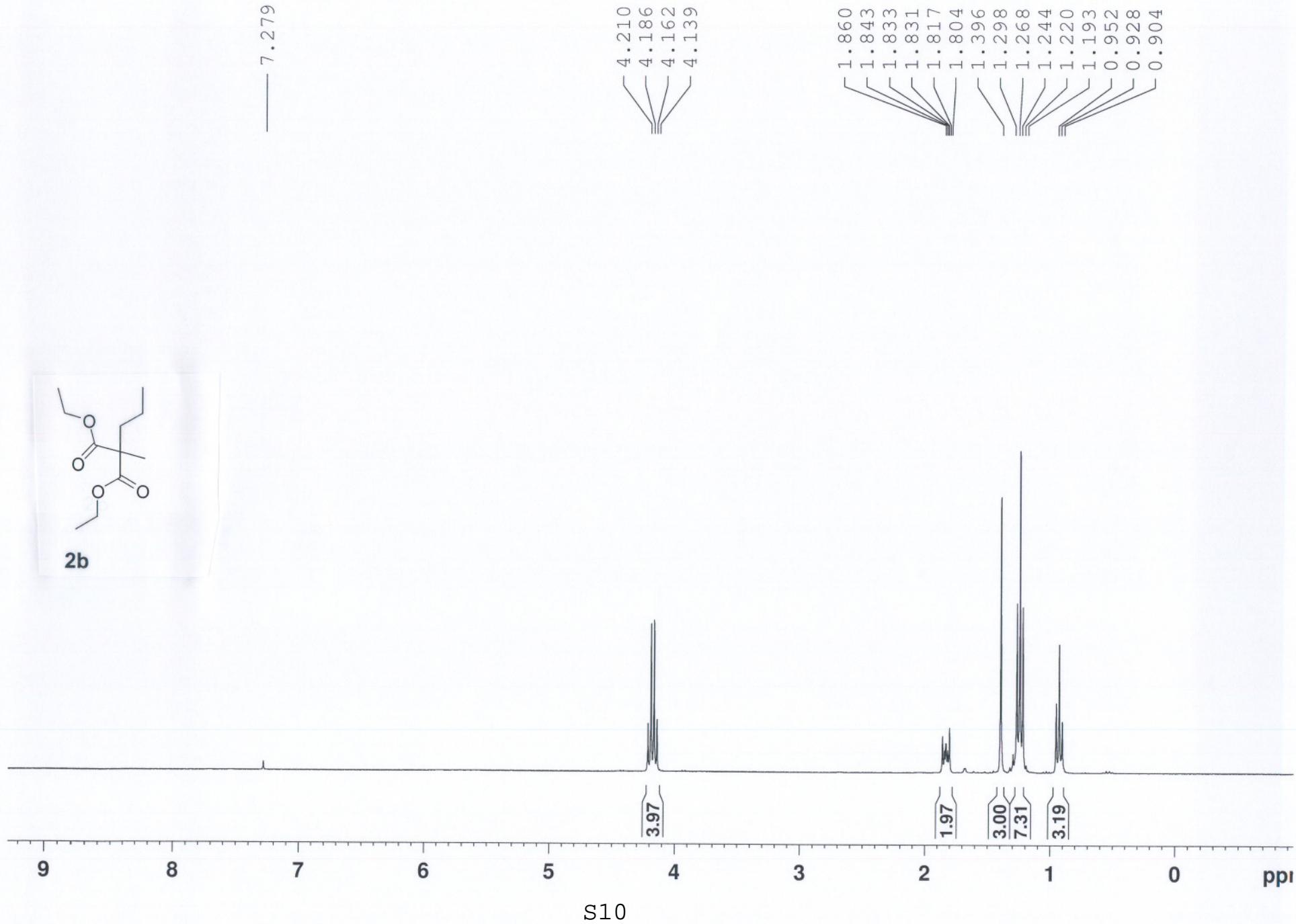
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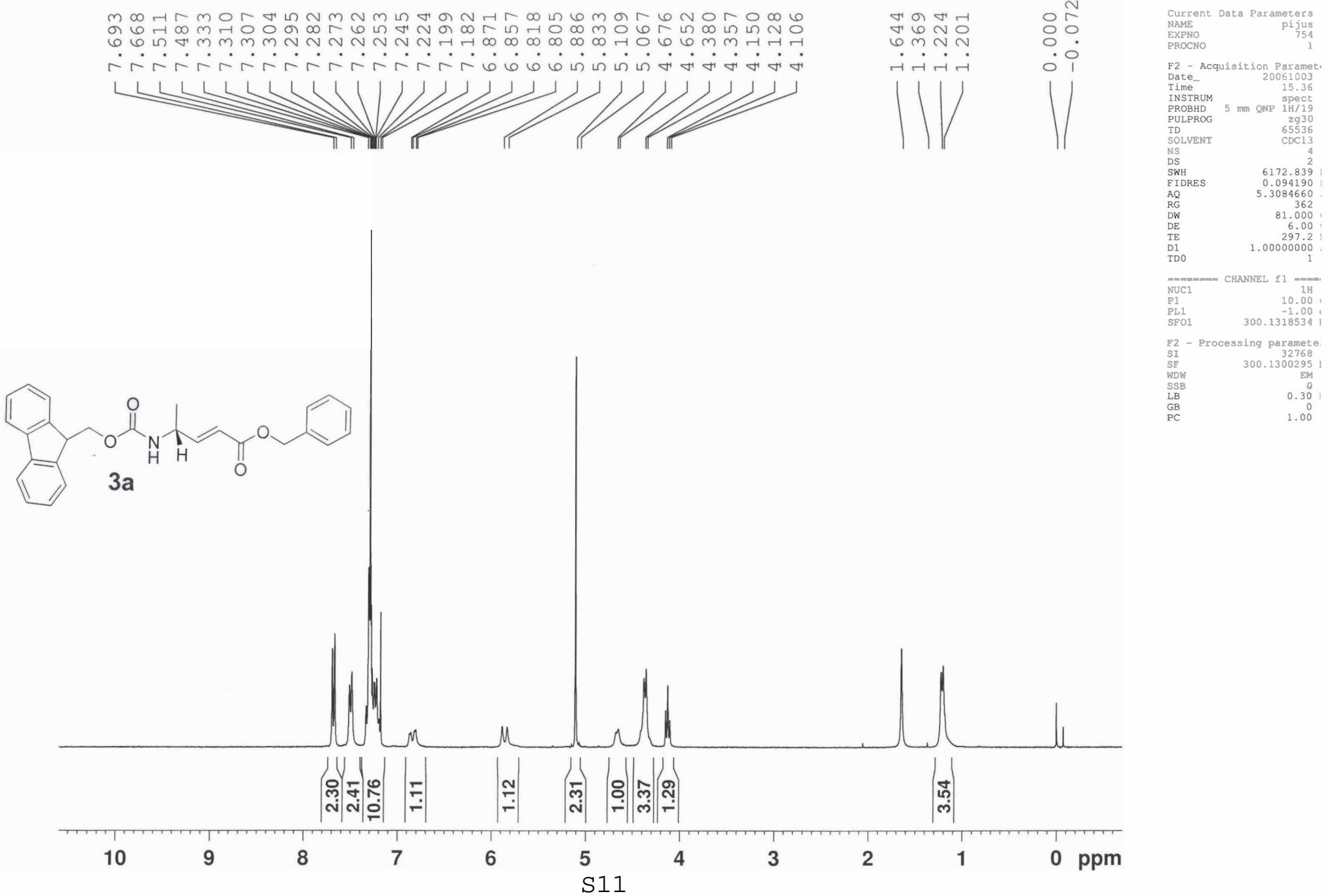


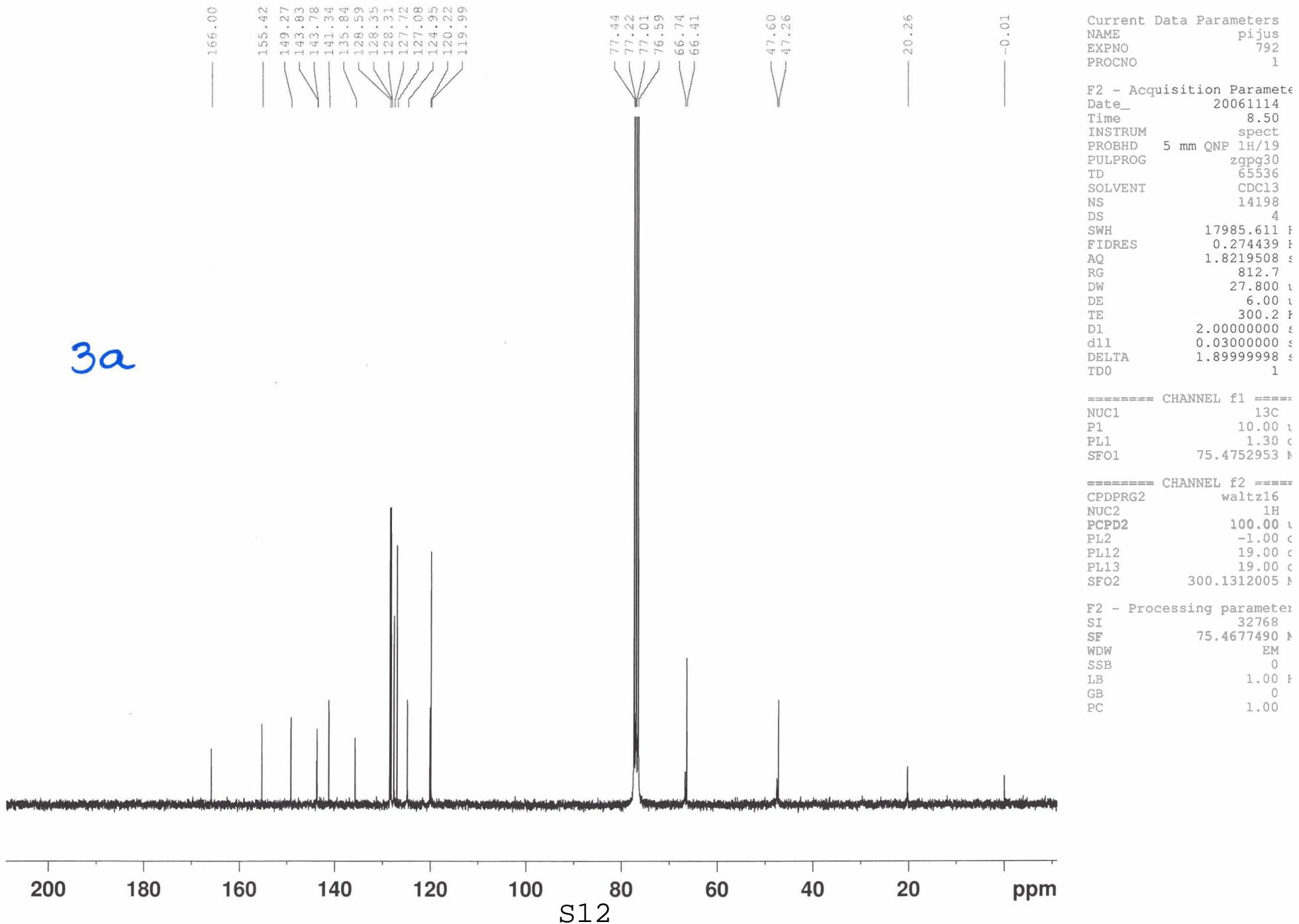
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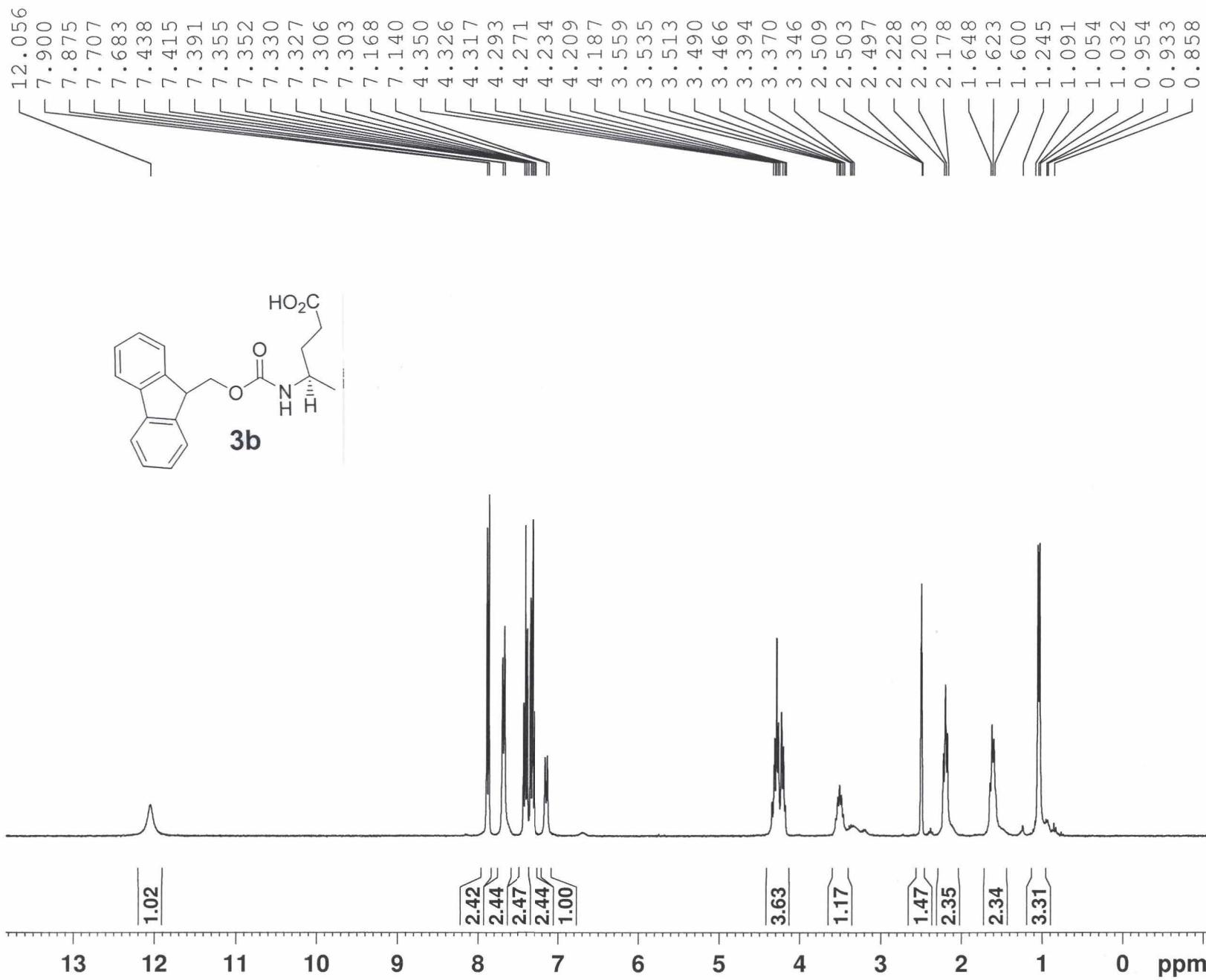


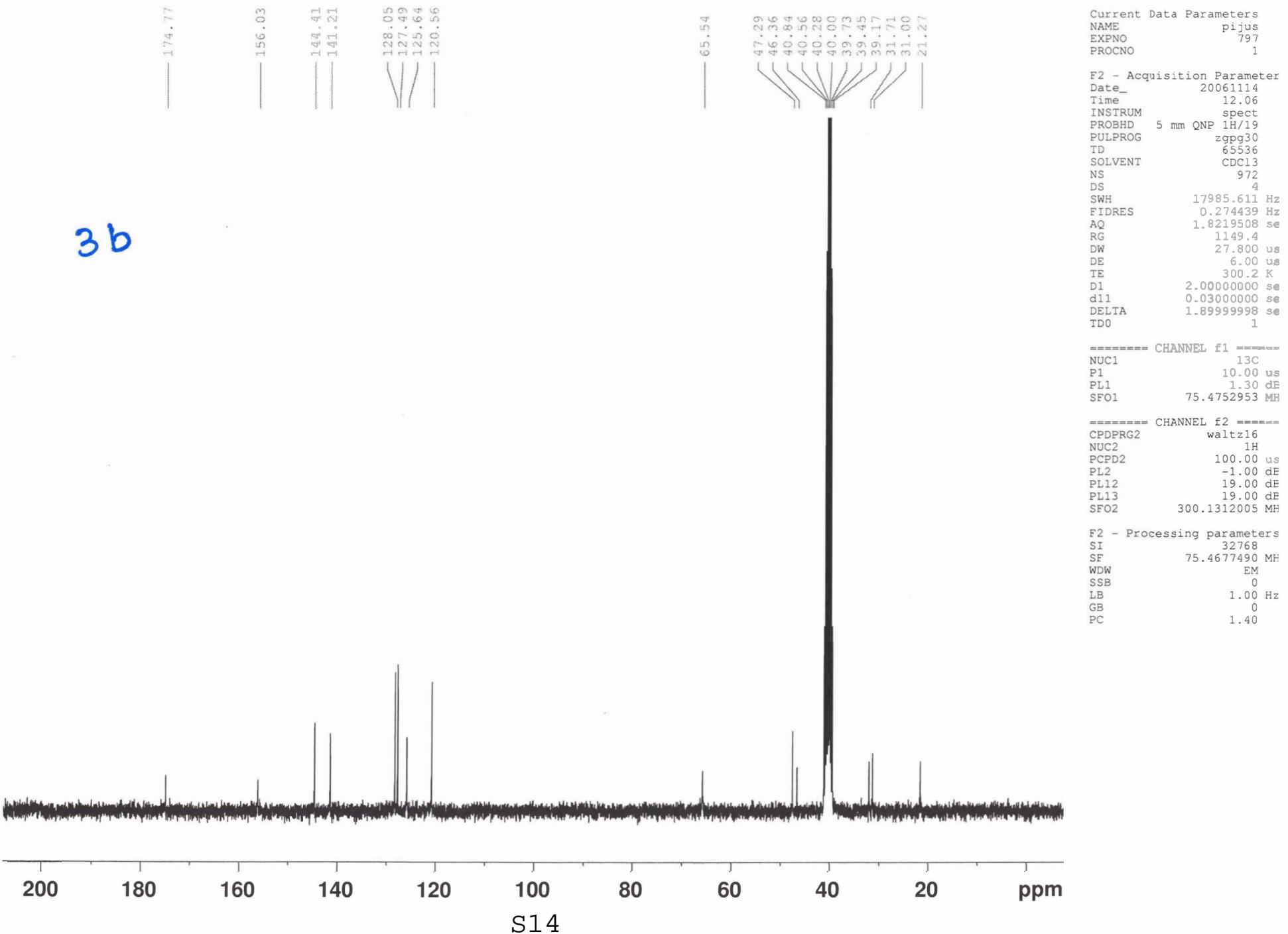
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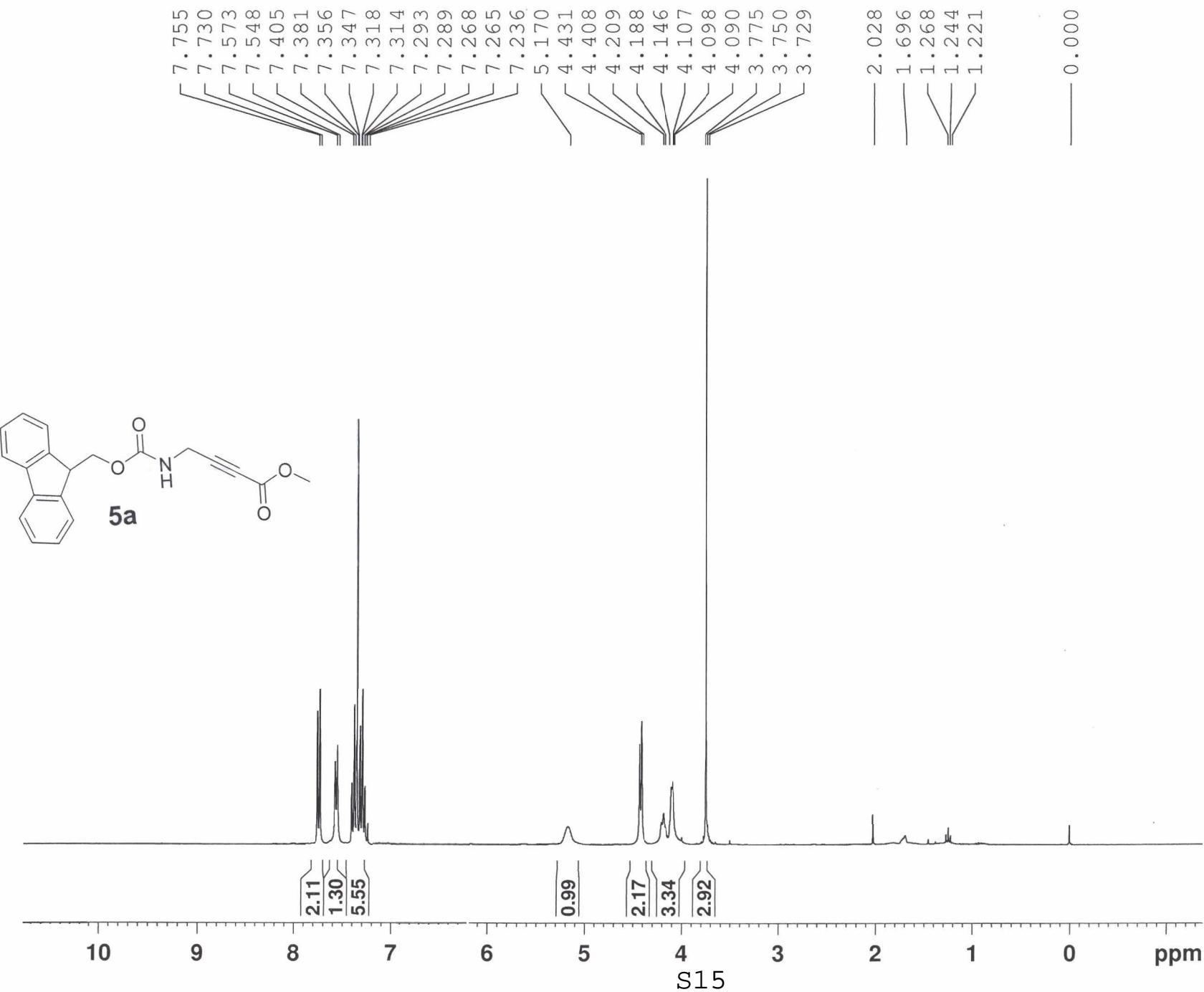










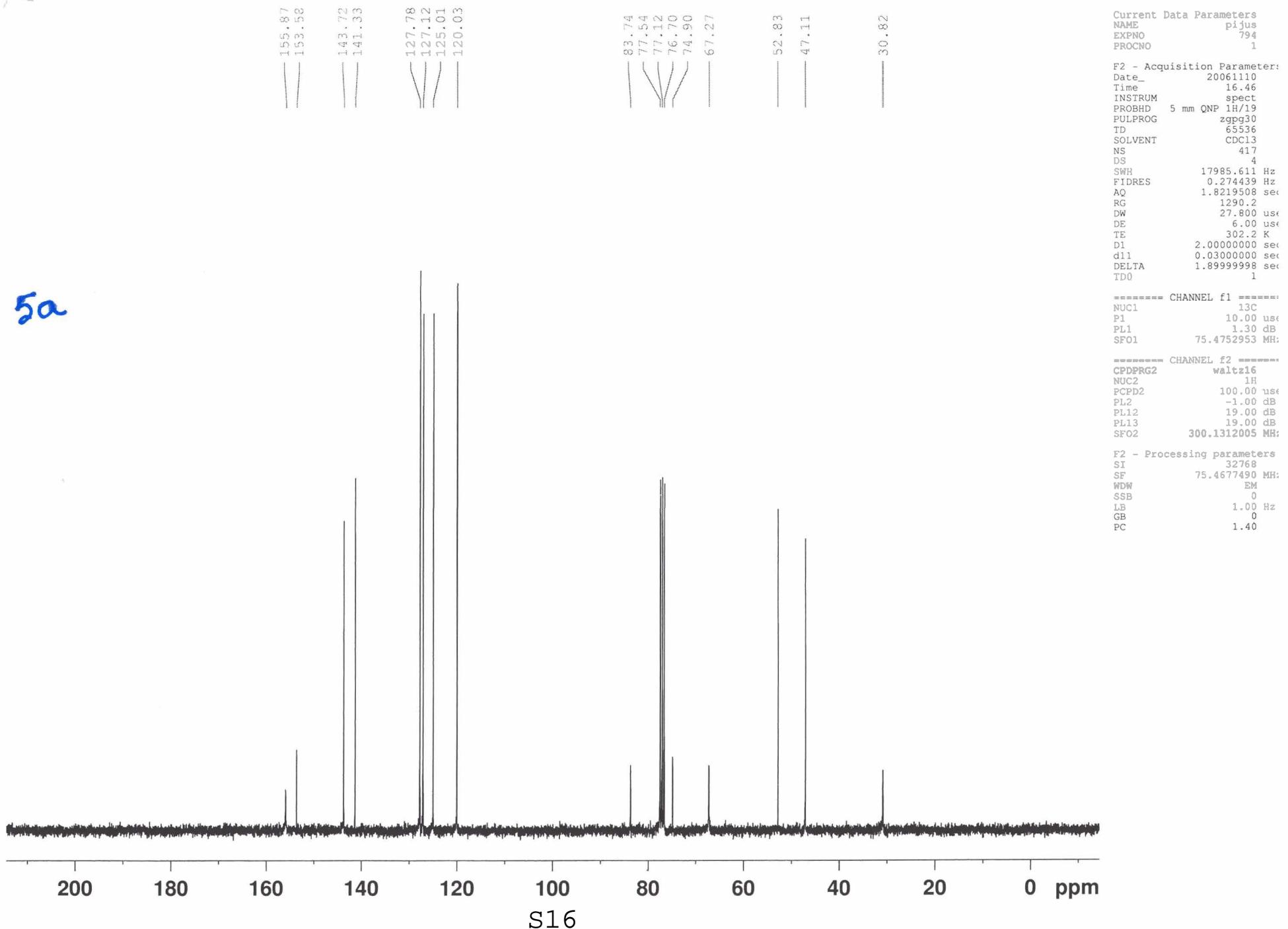


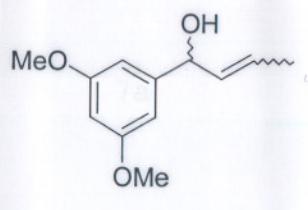
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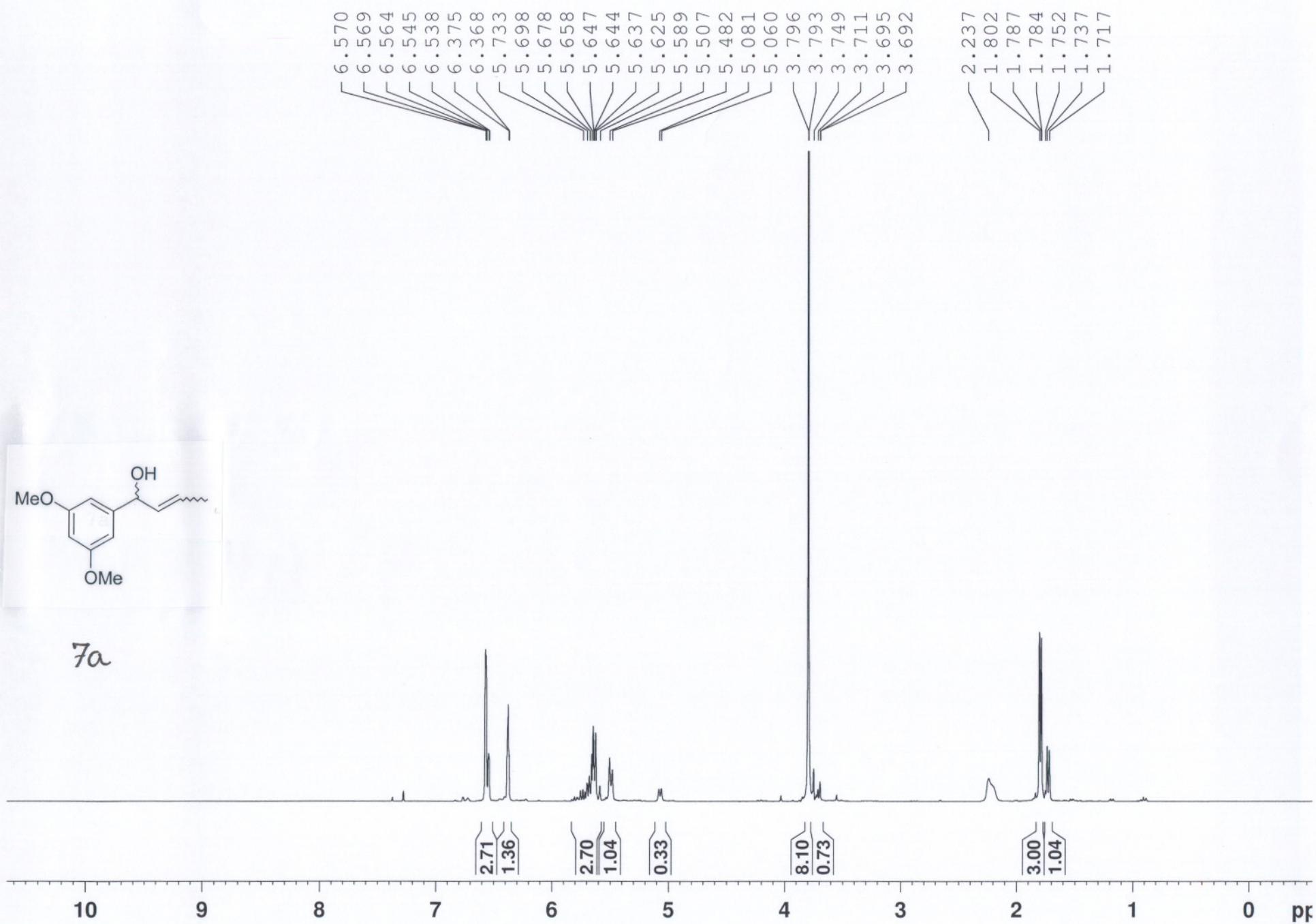
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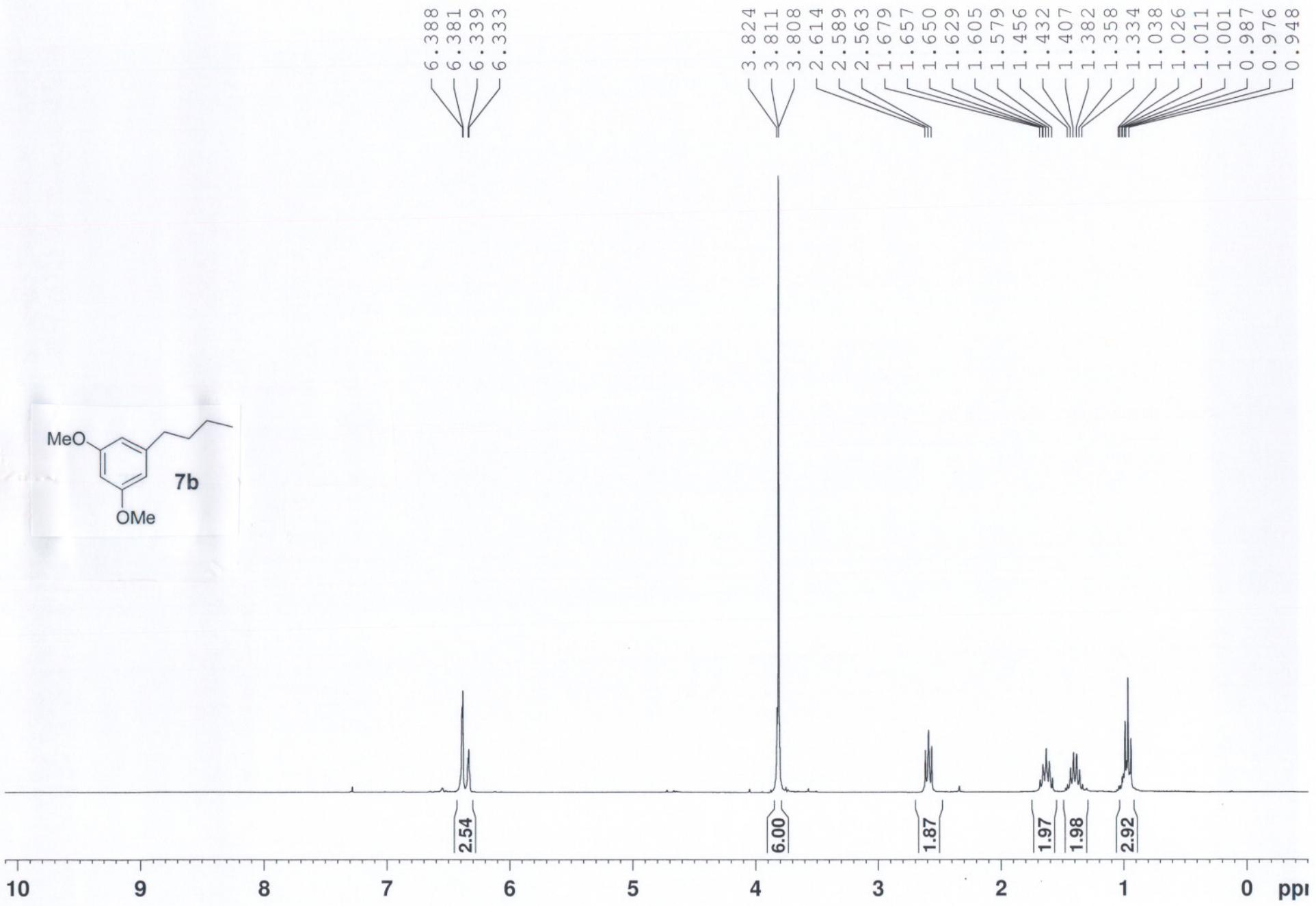
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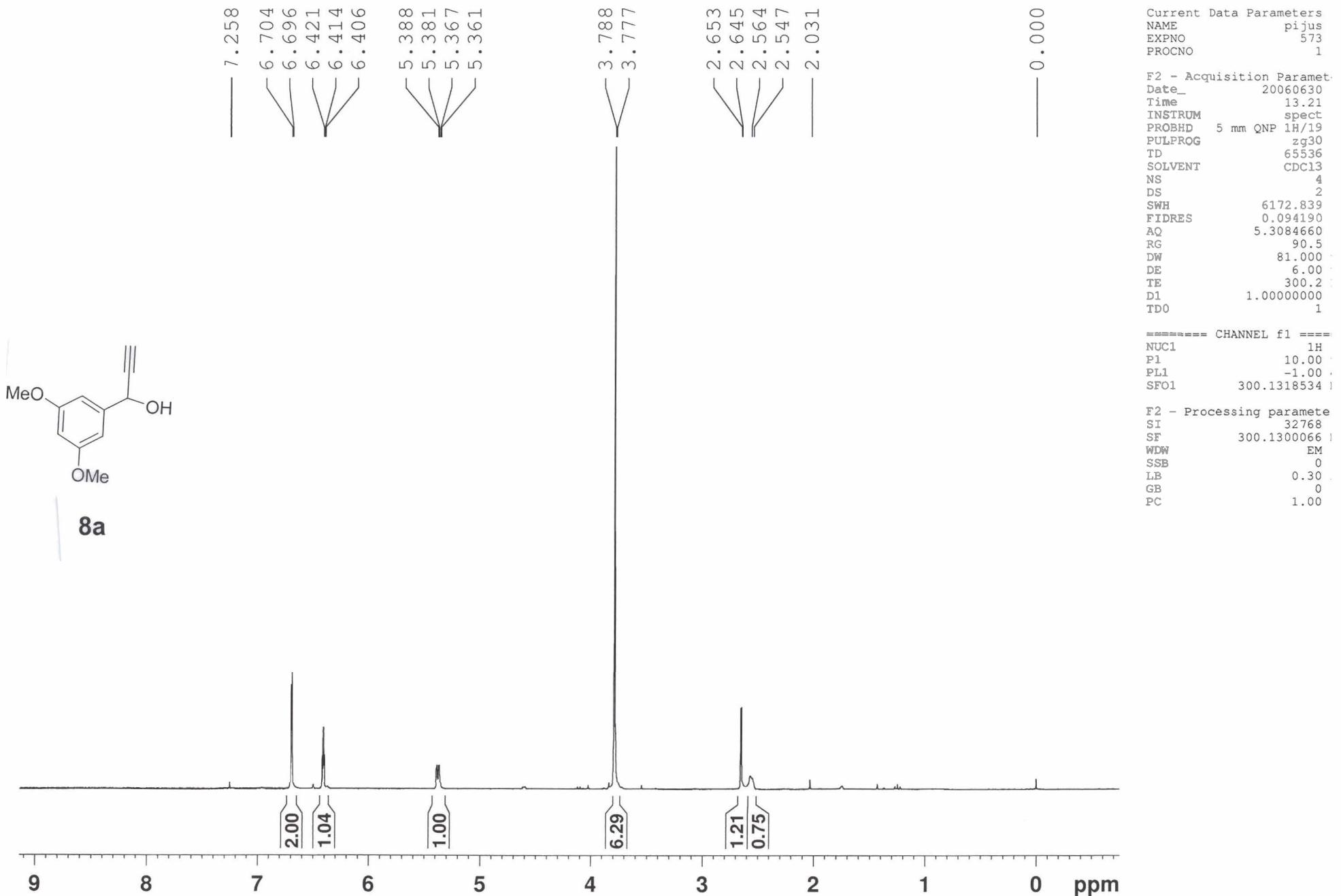


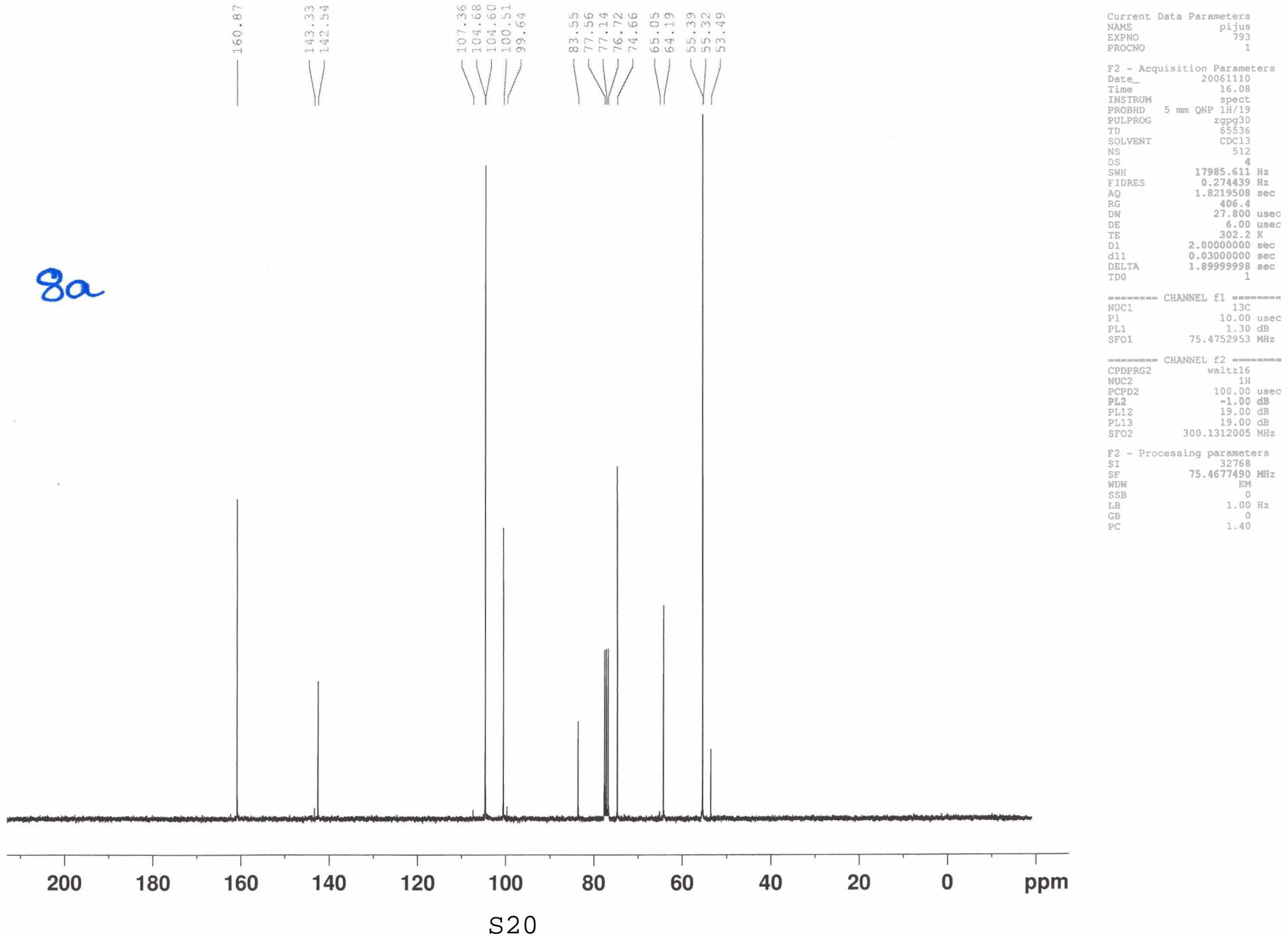


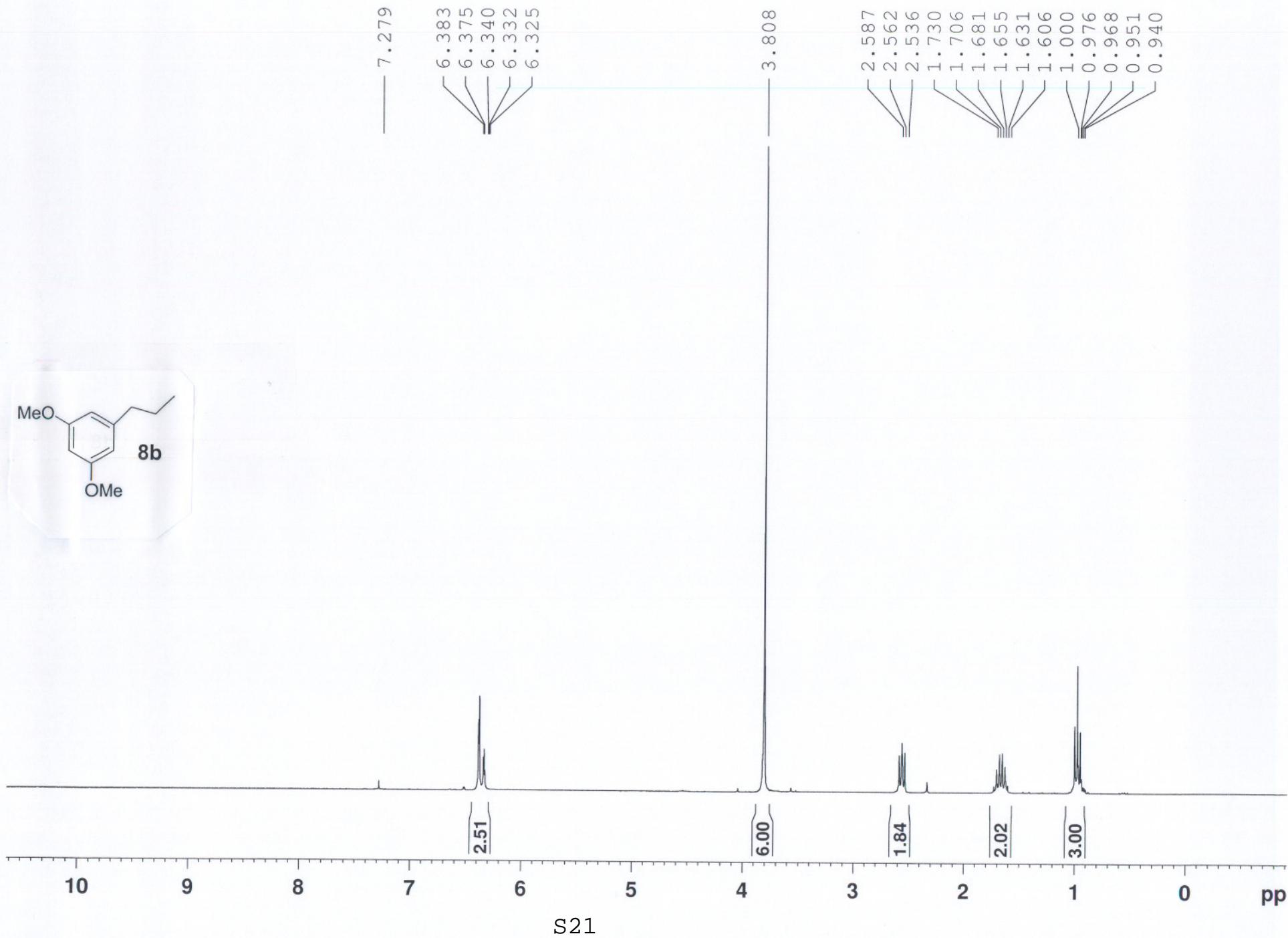
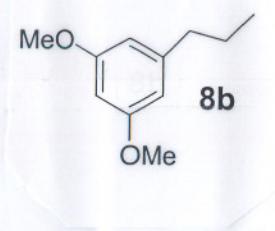
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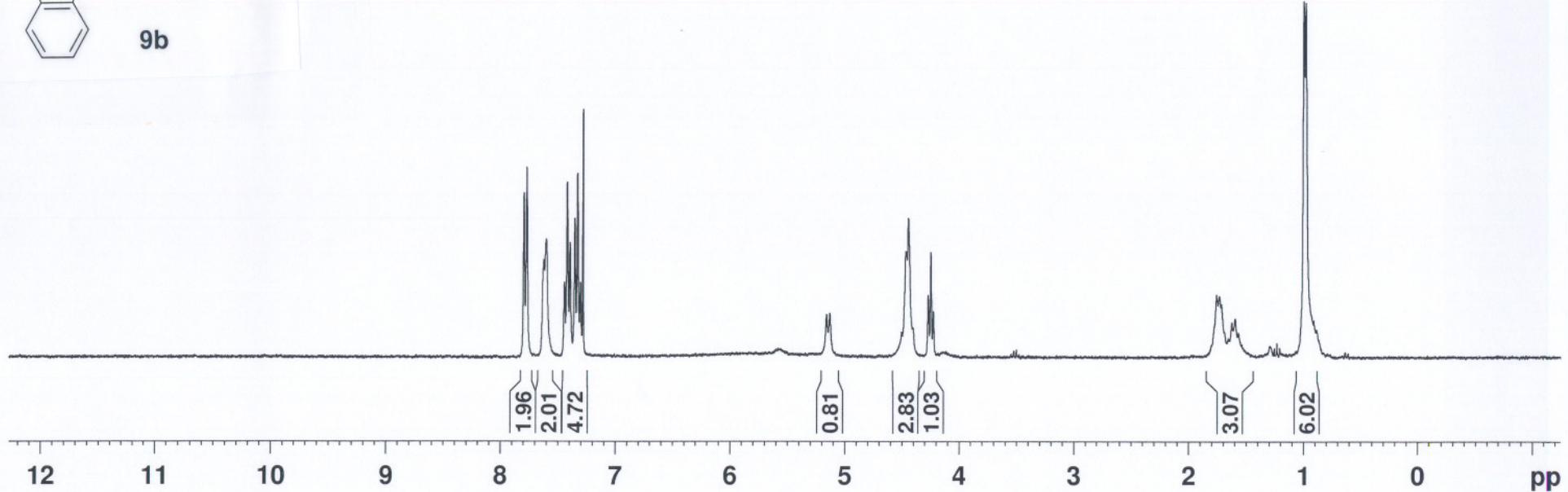
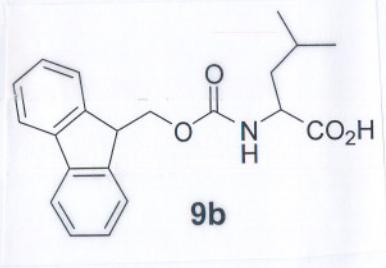


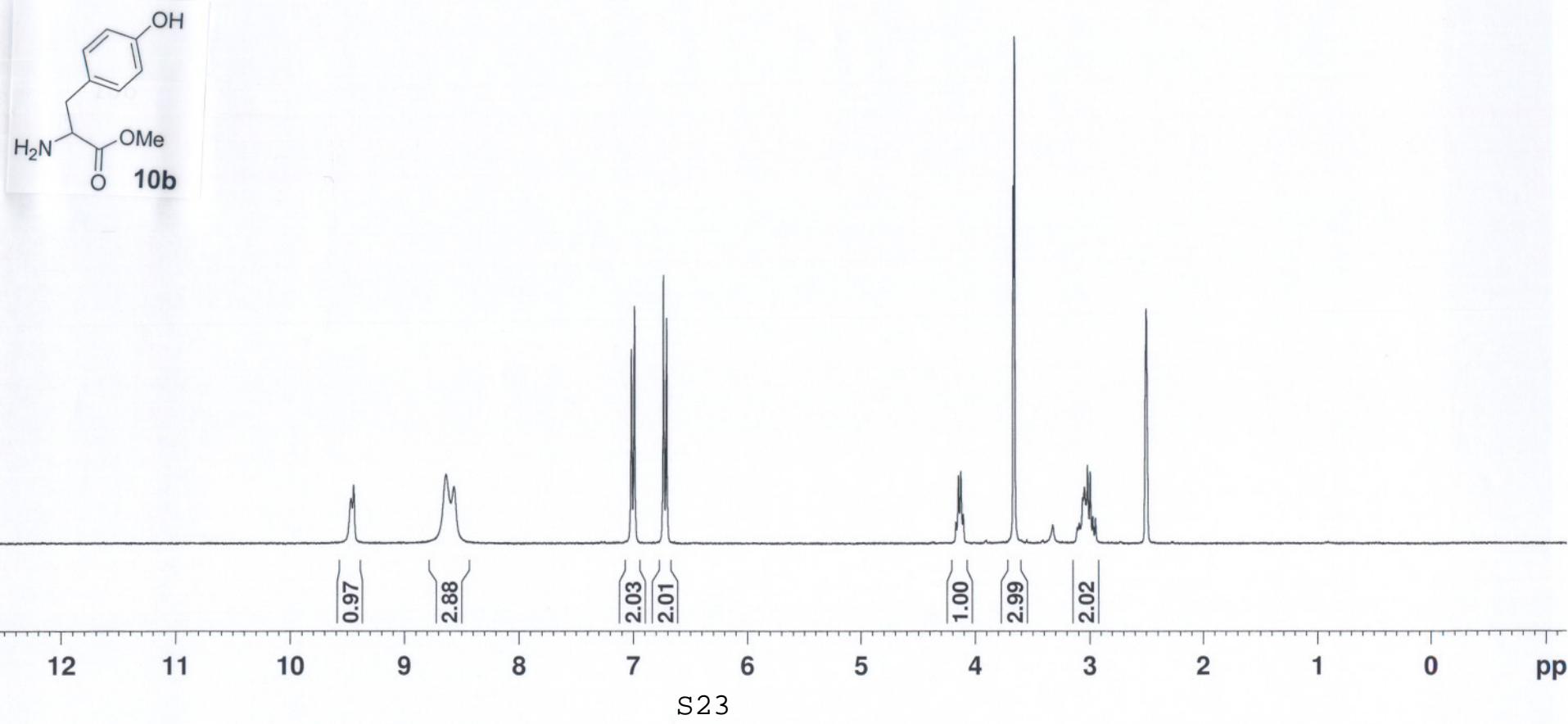


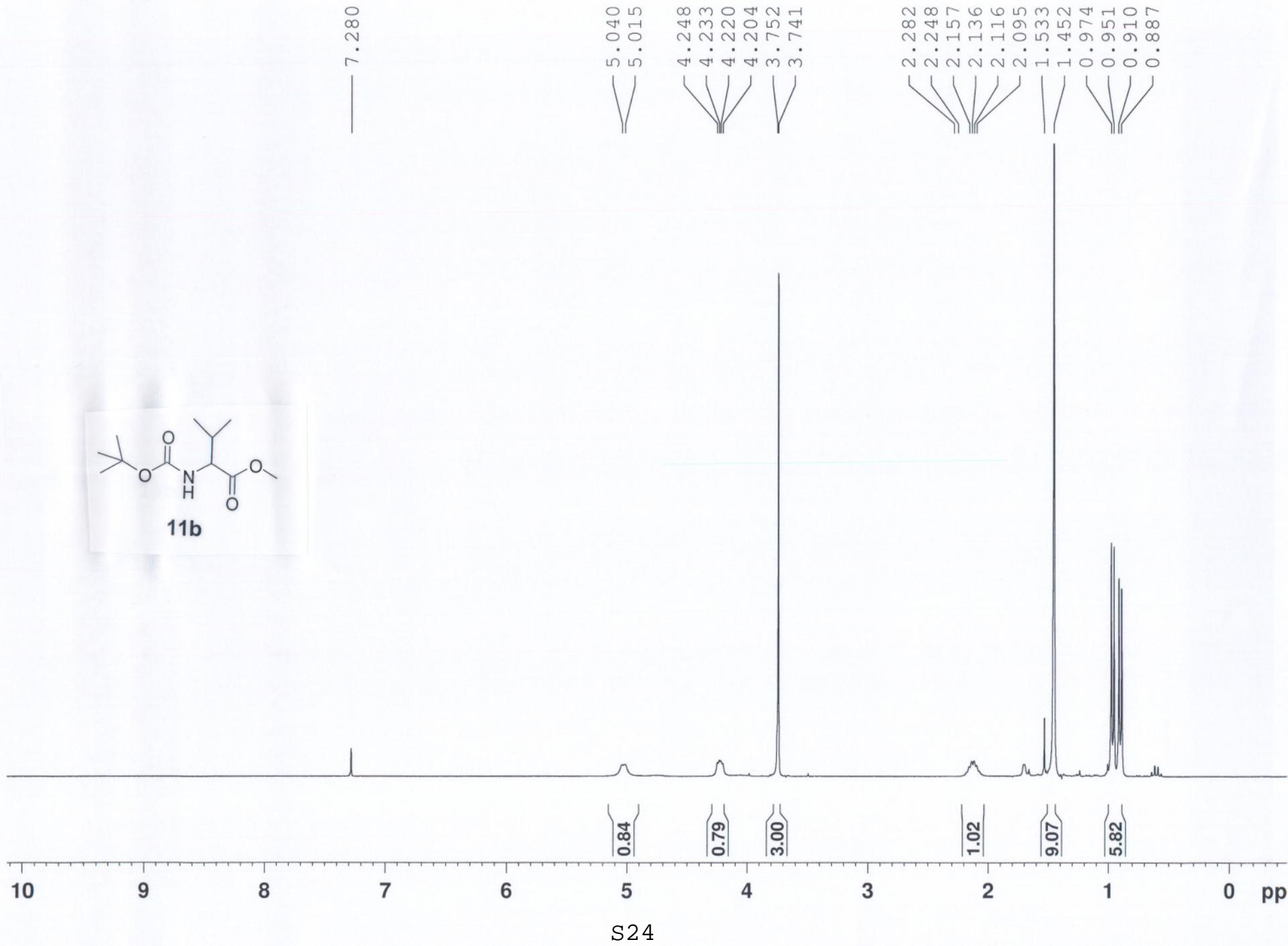


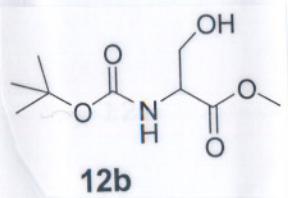


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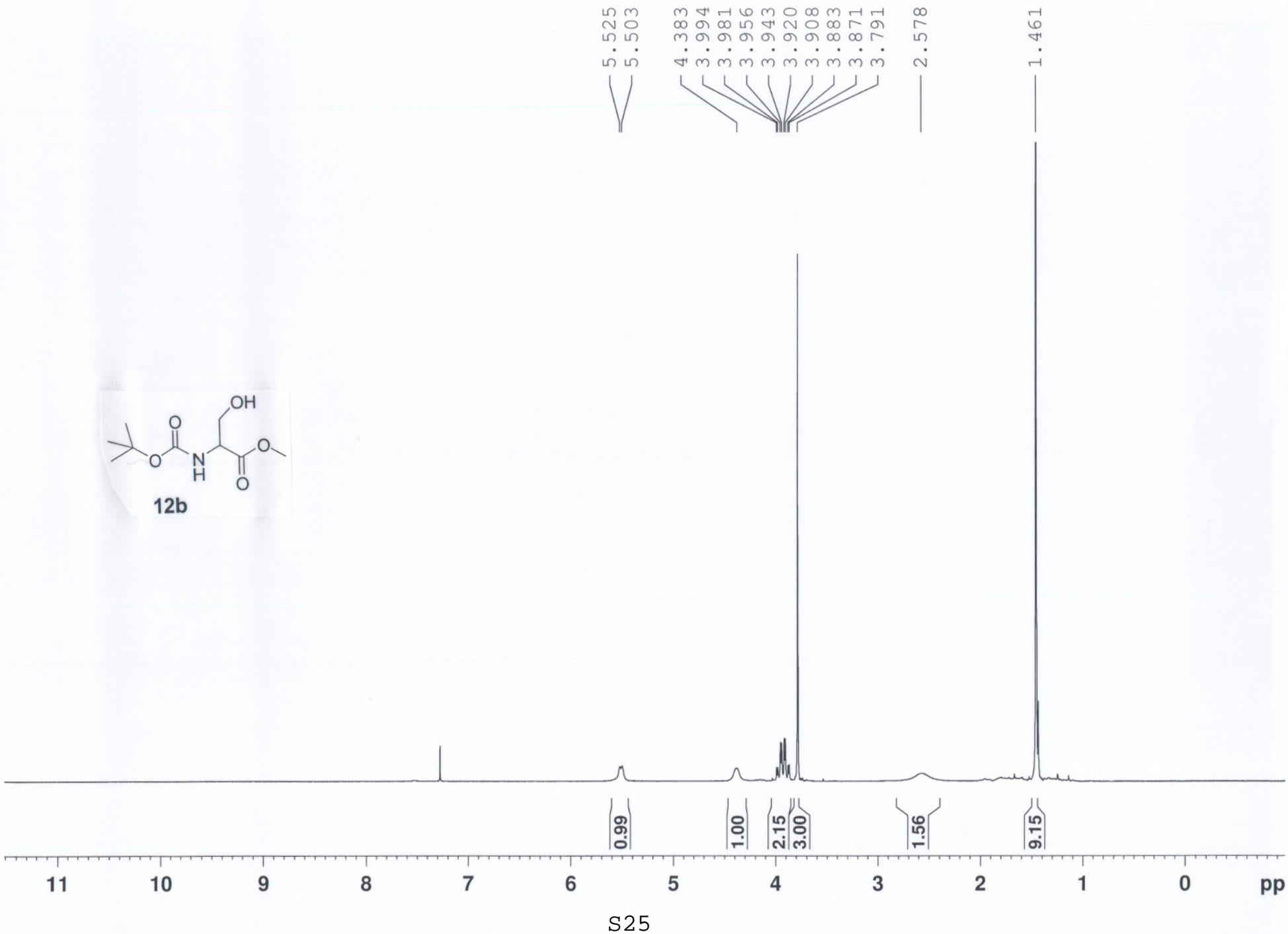


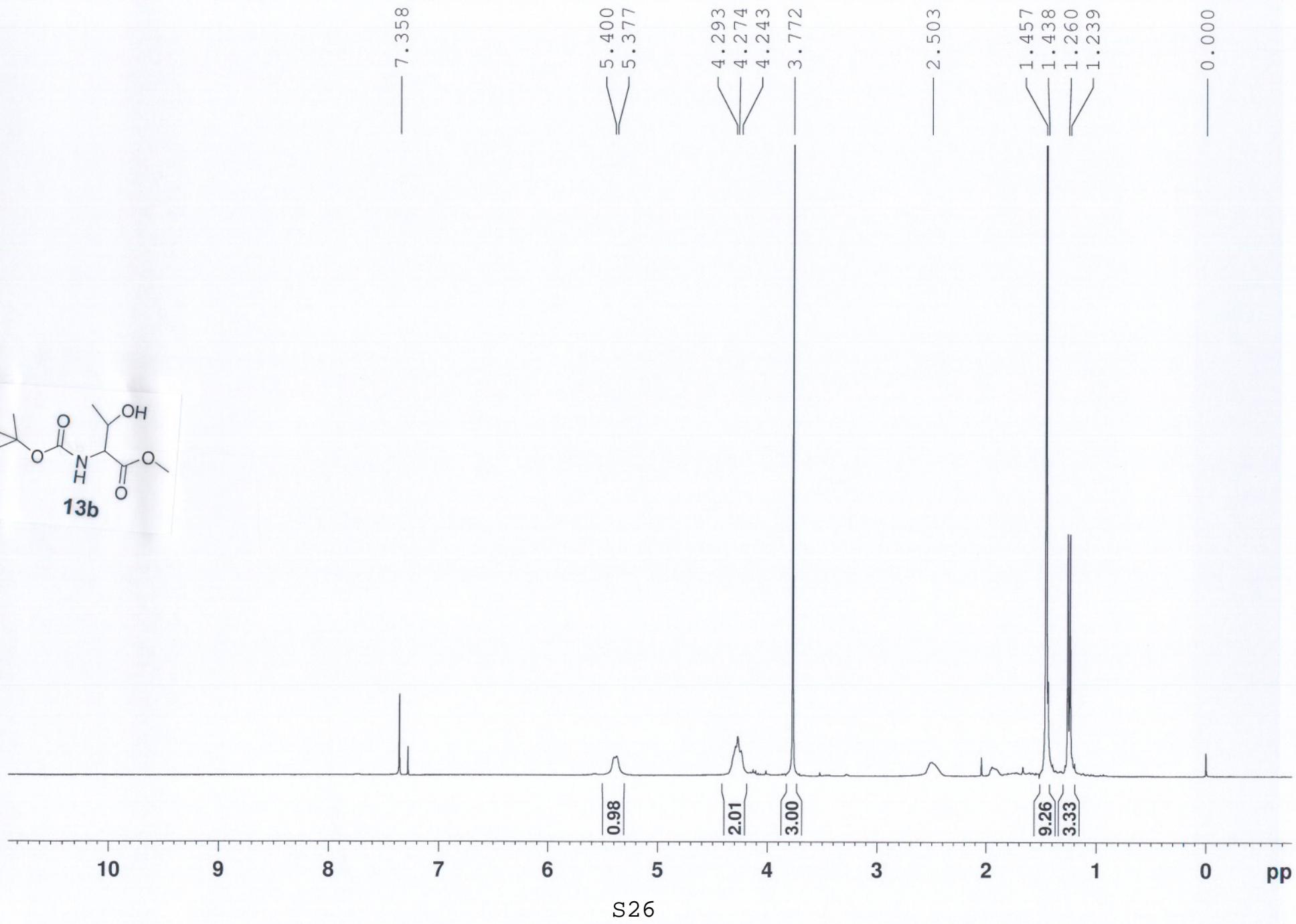
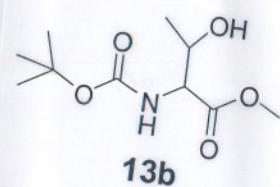




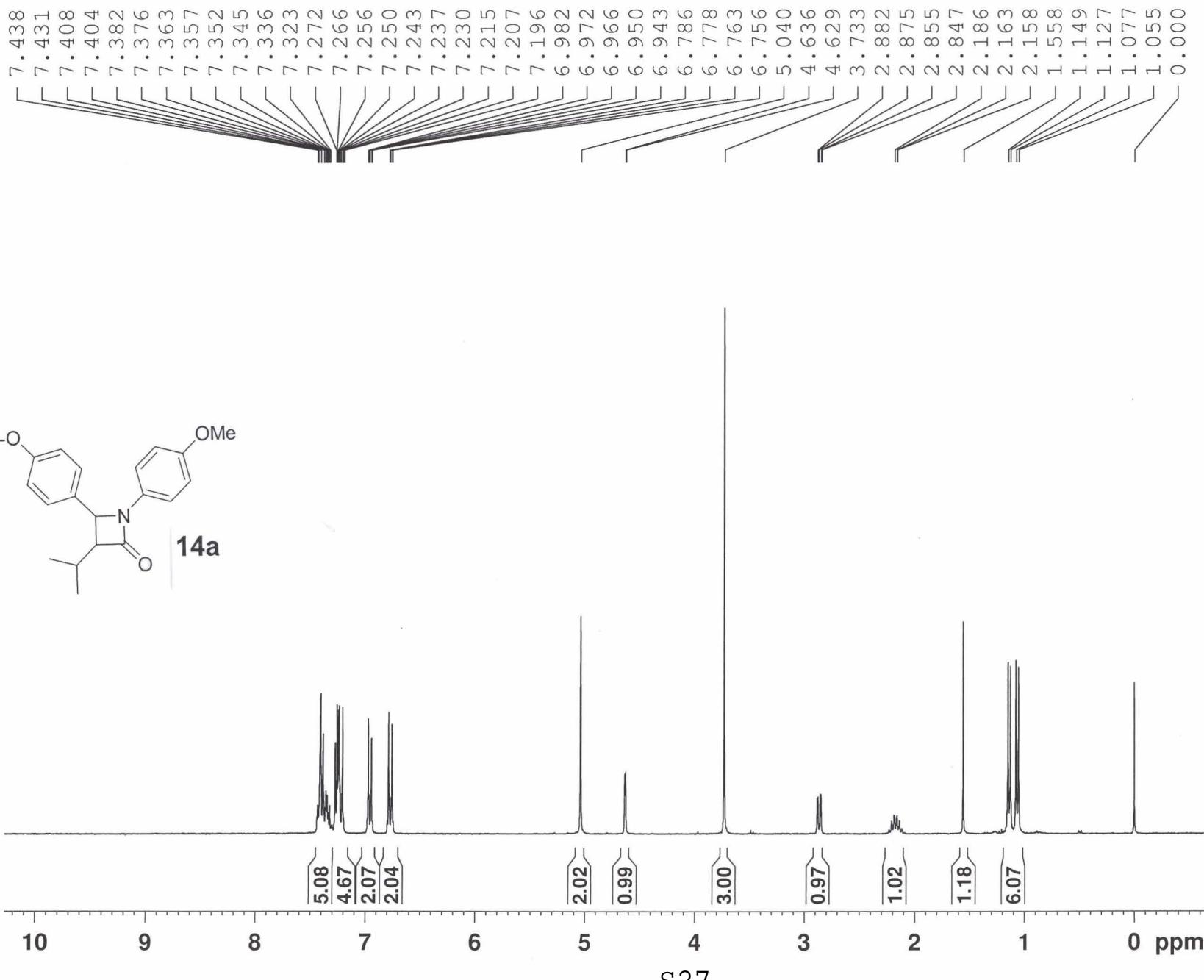


12b





S26

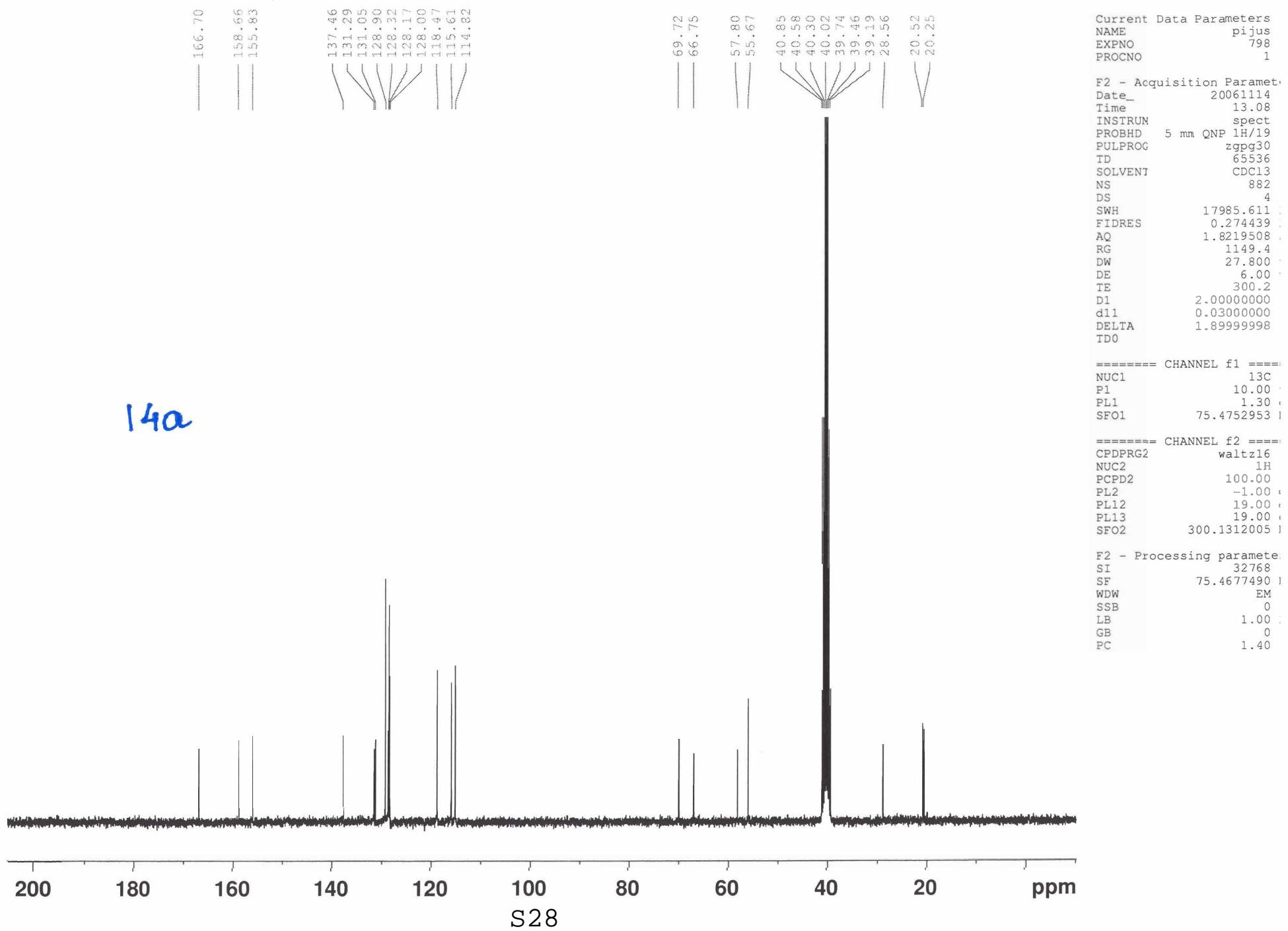


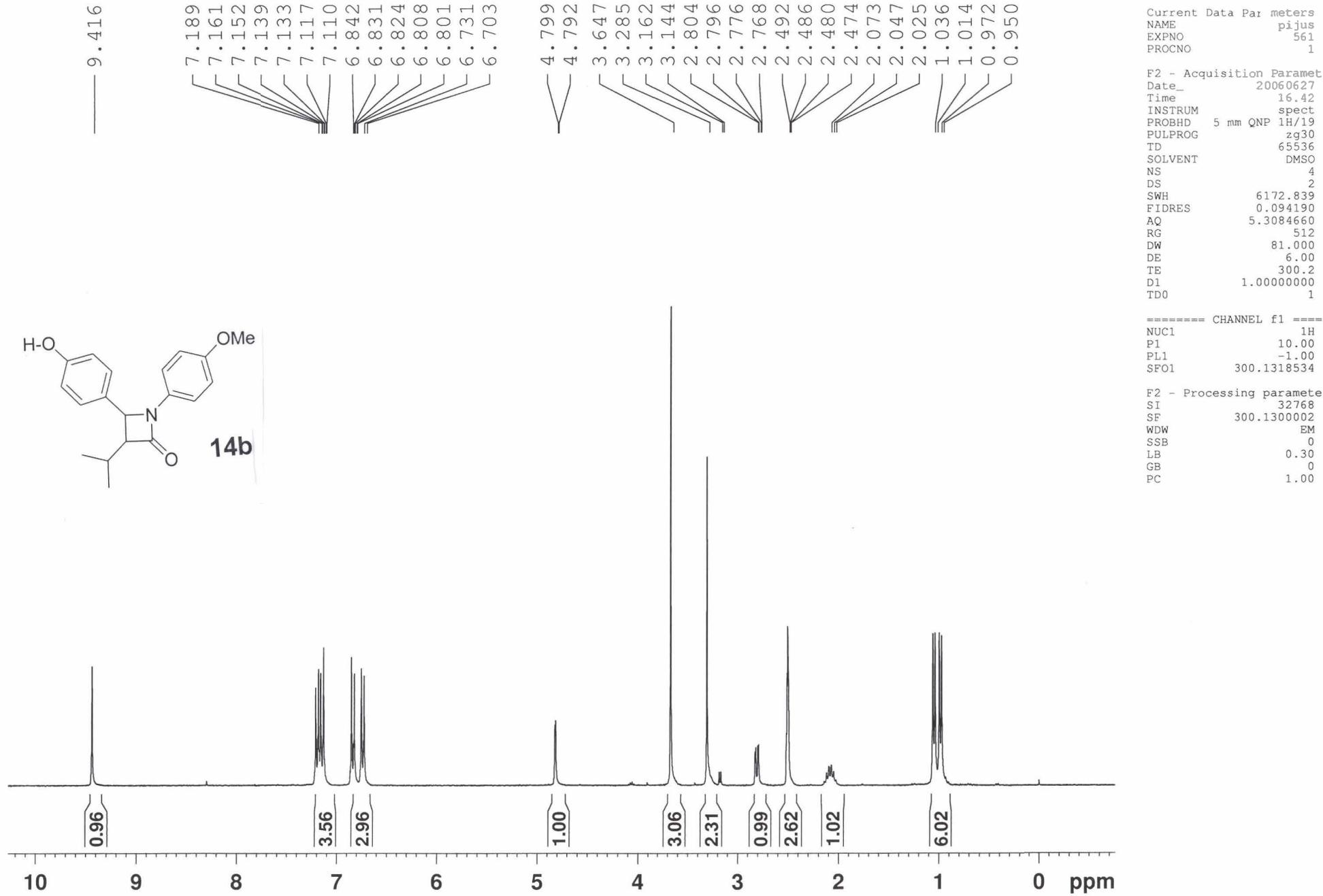
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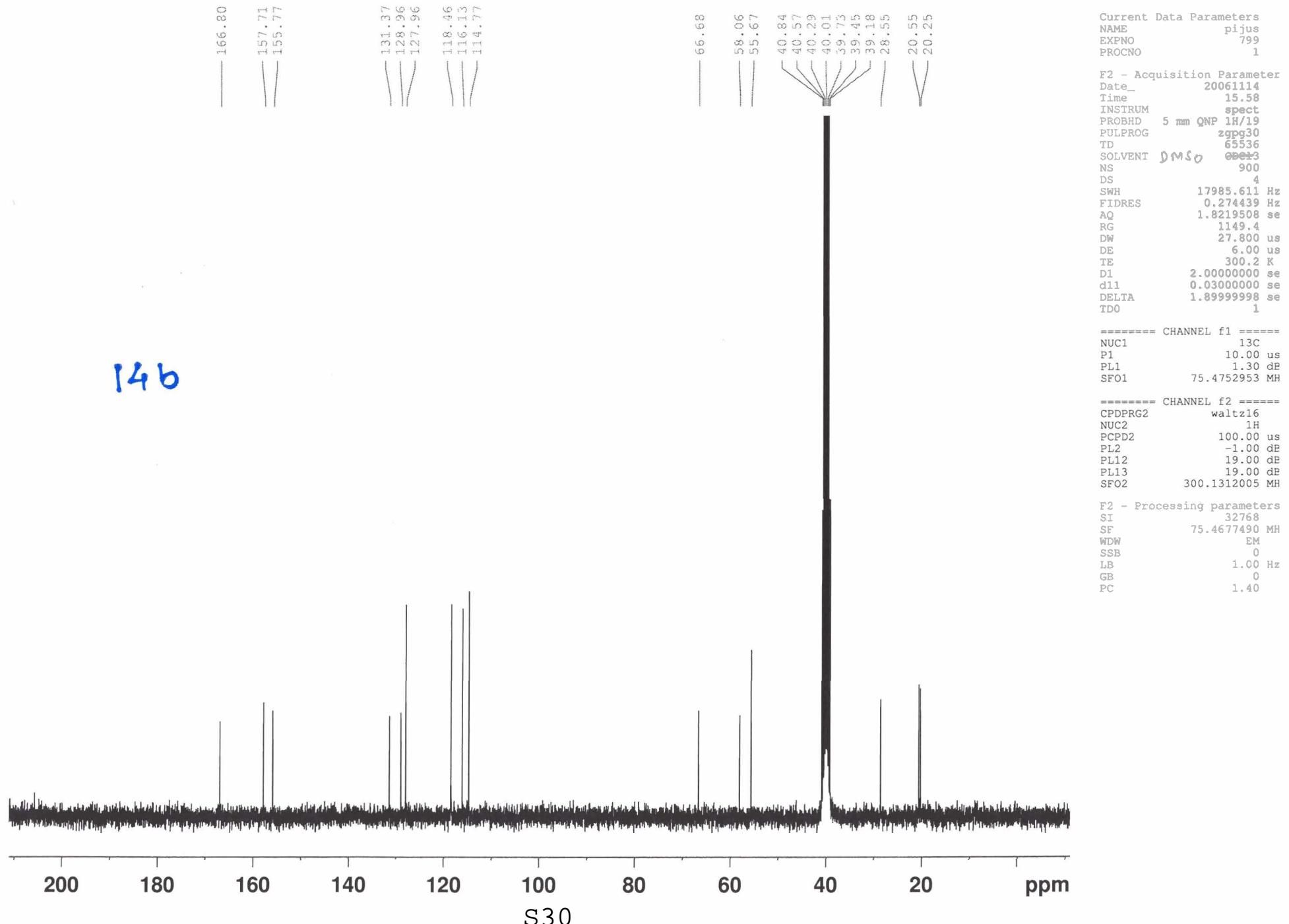
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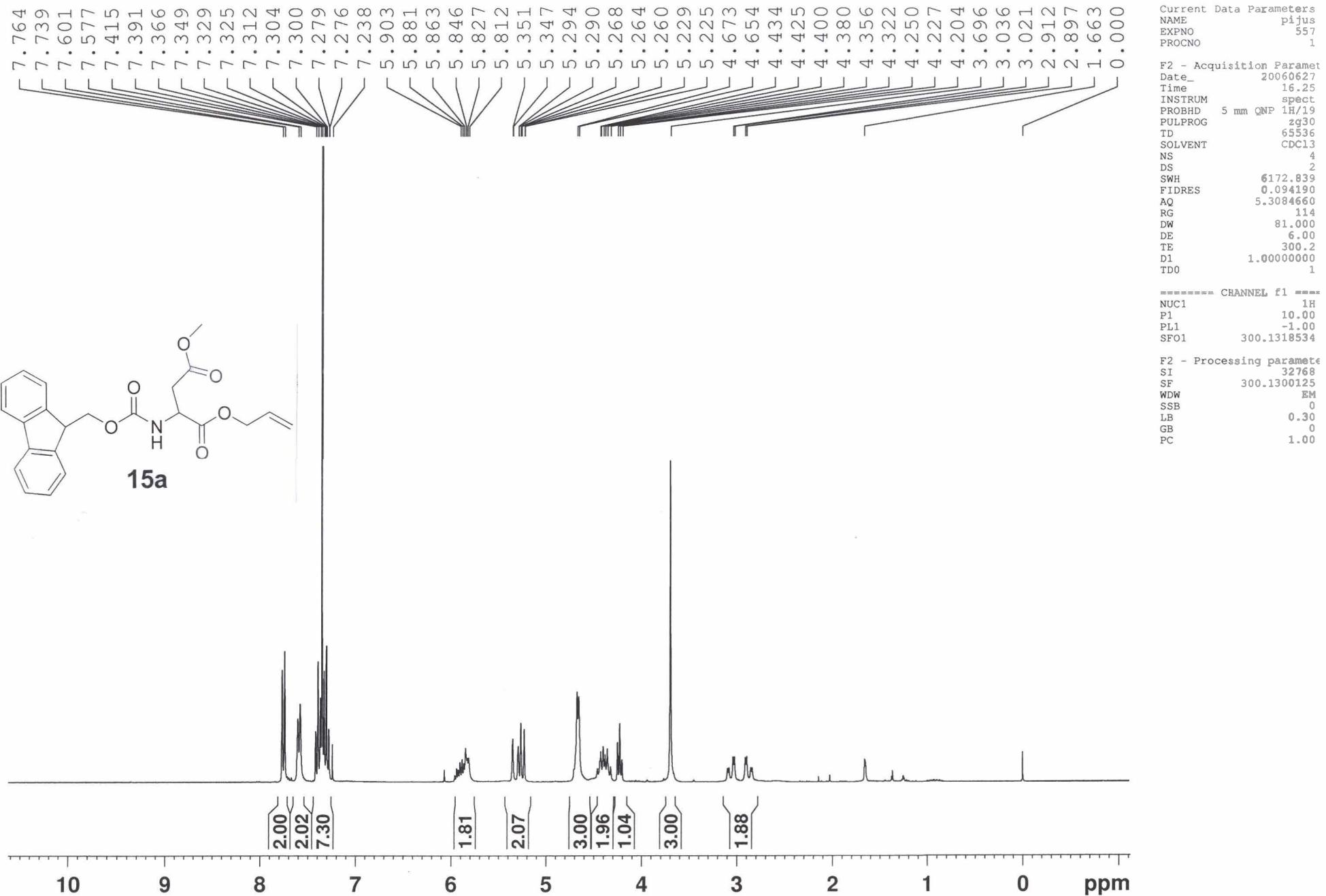
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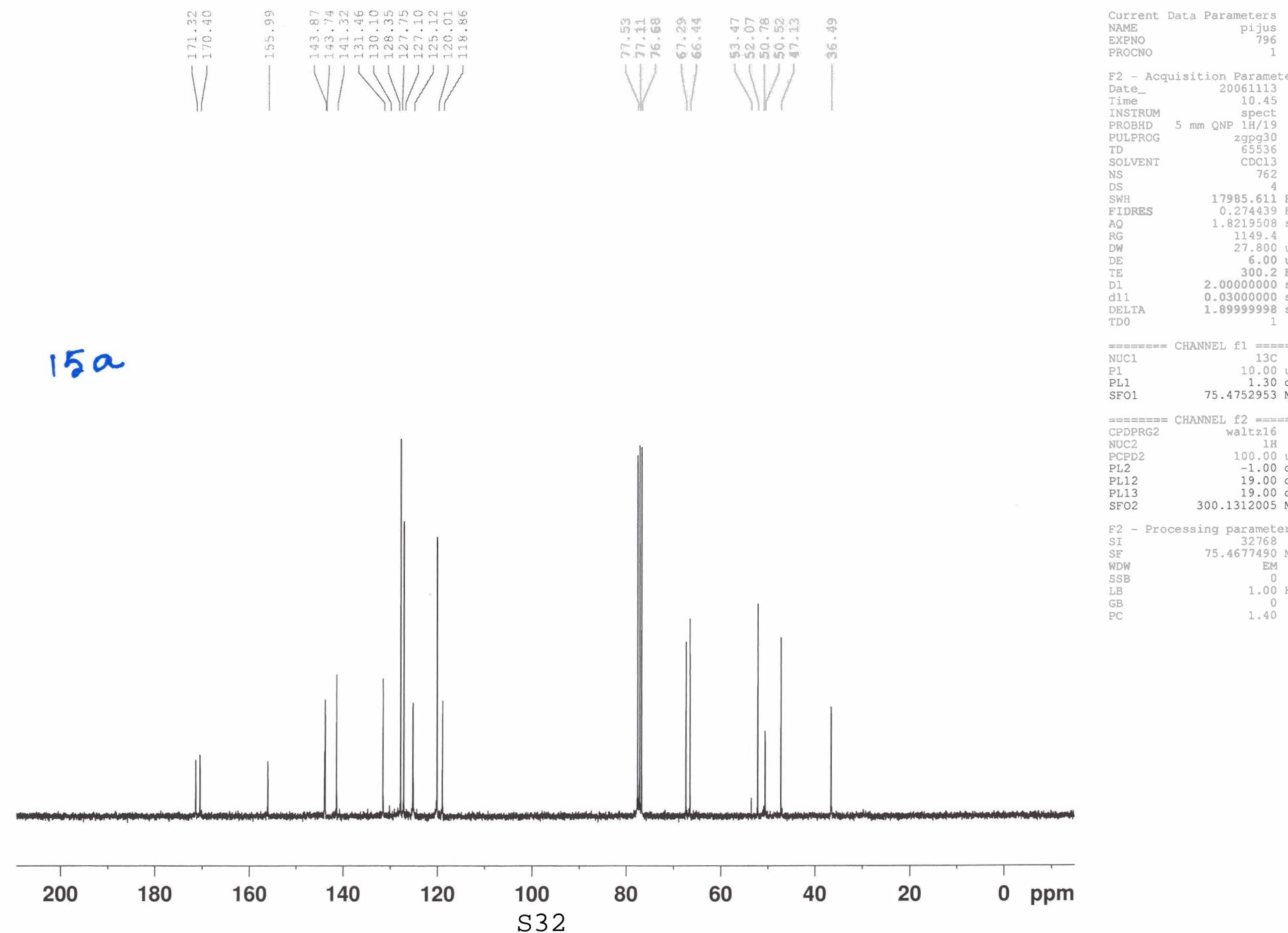


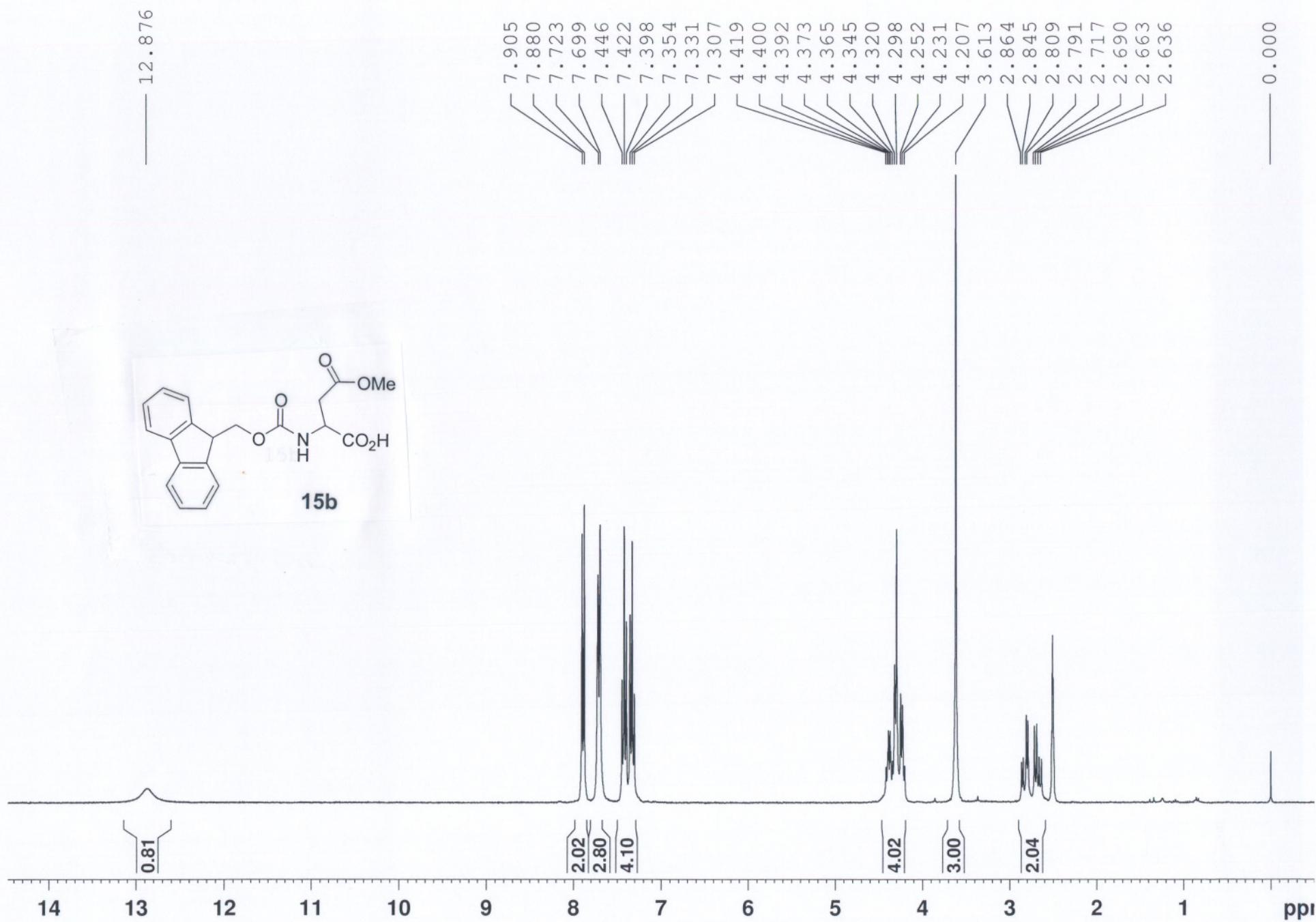


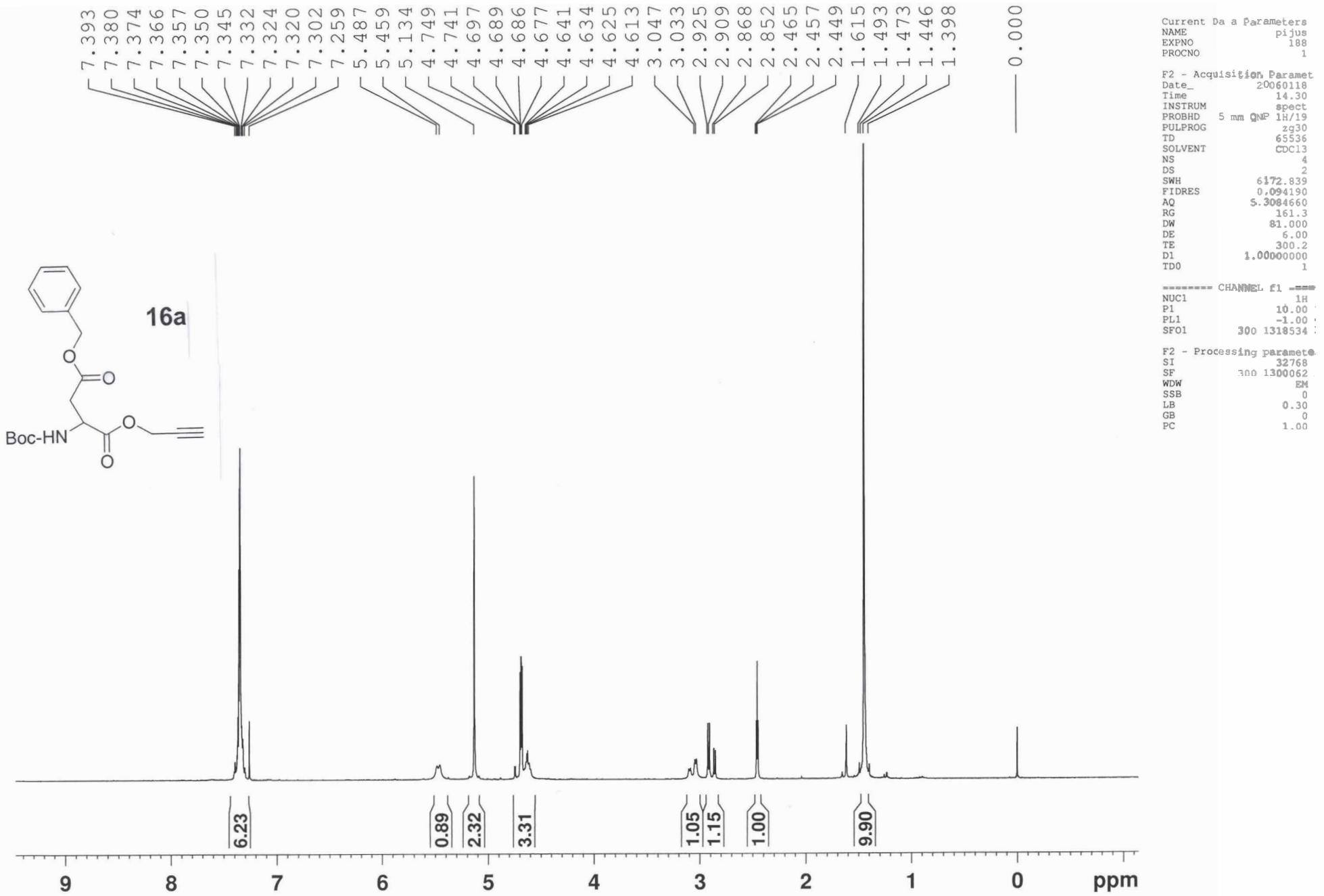


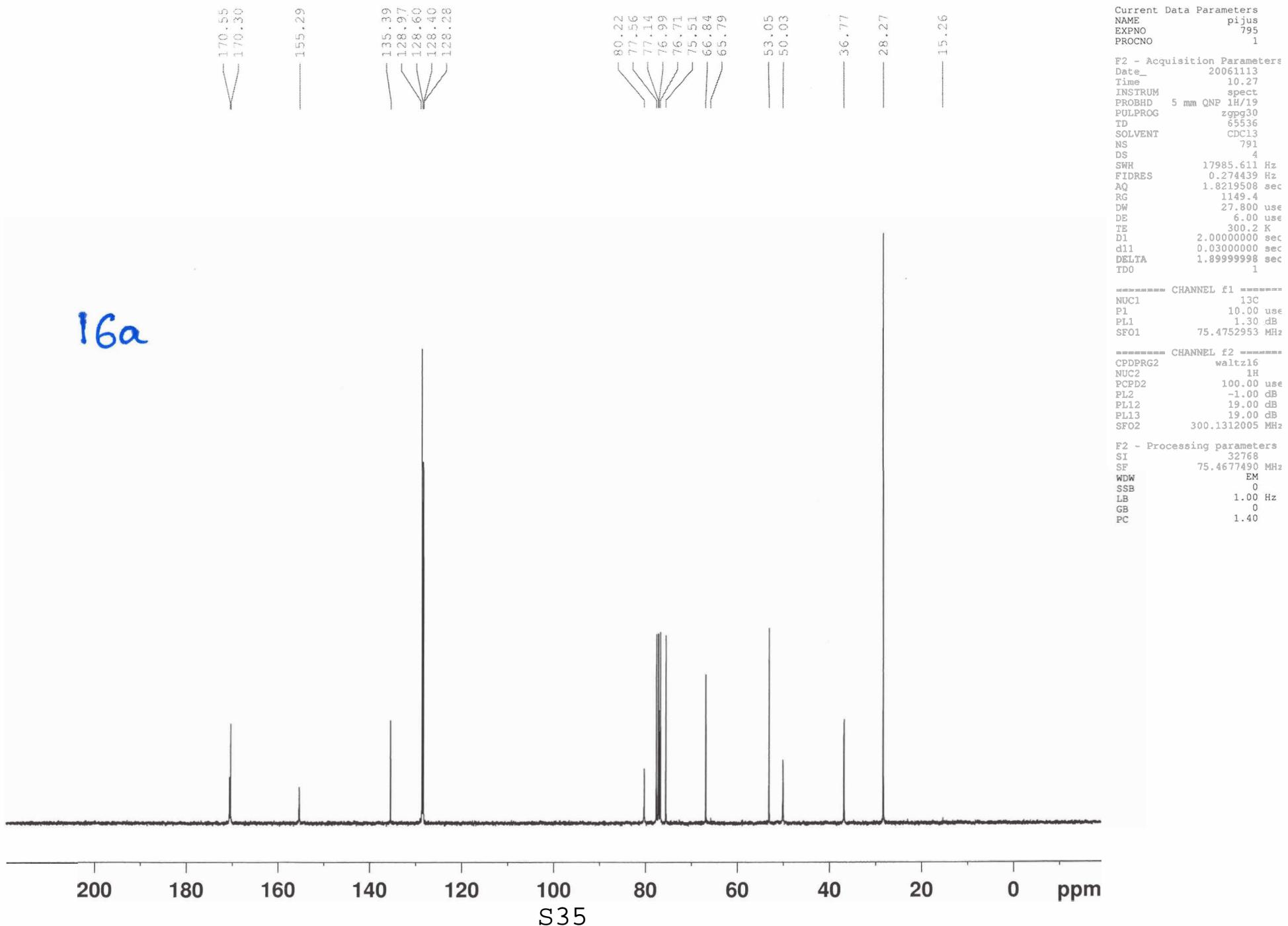


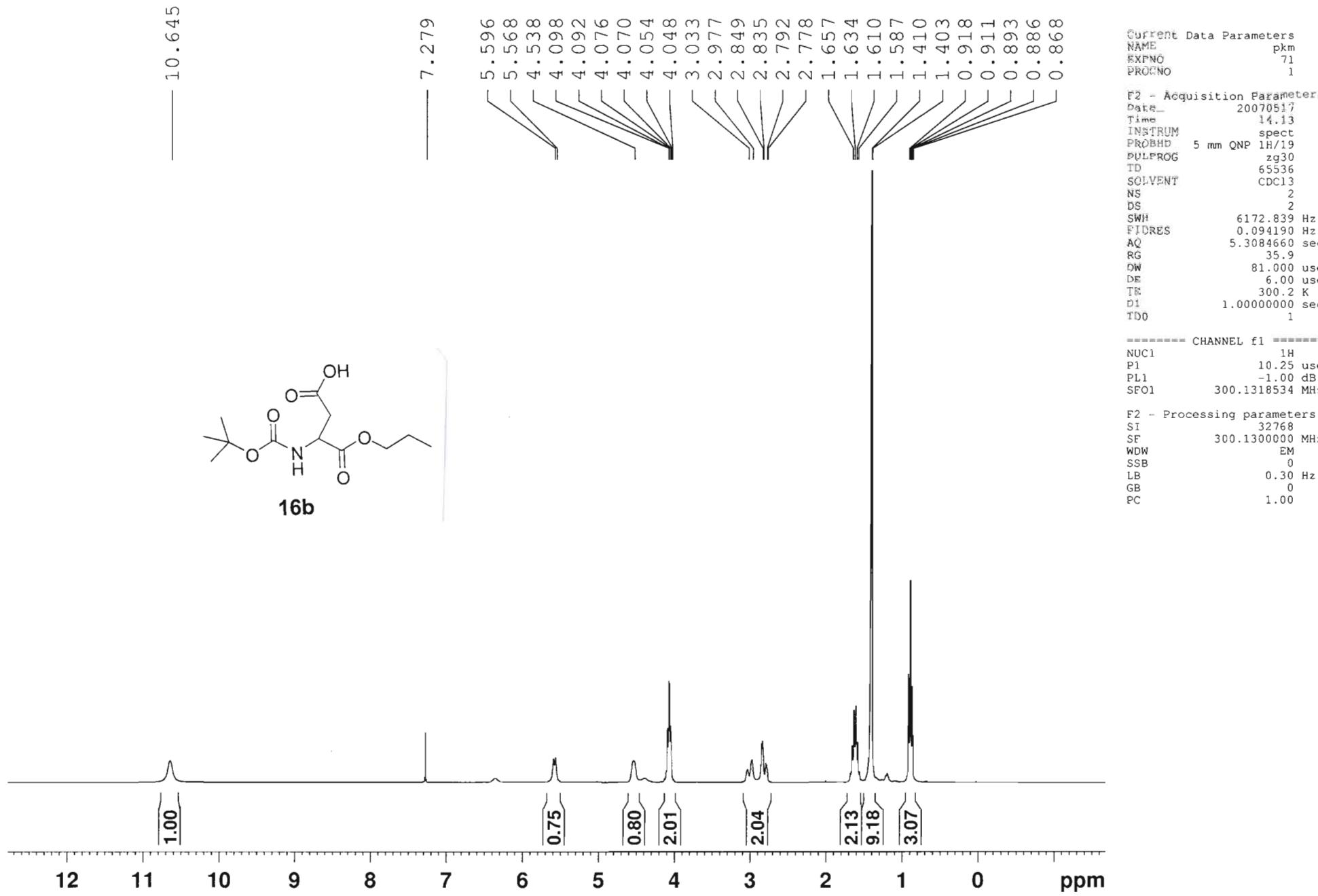
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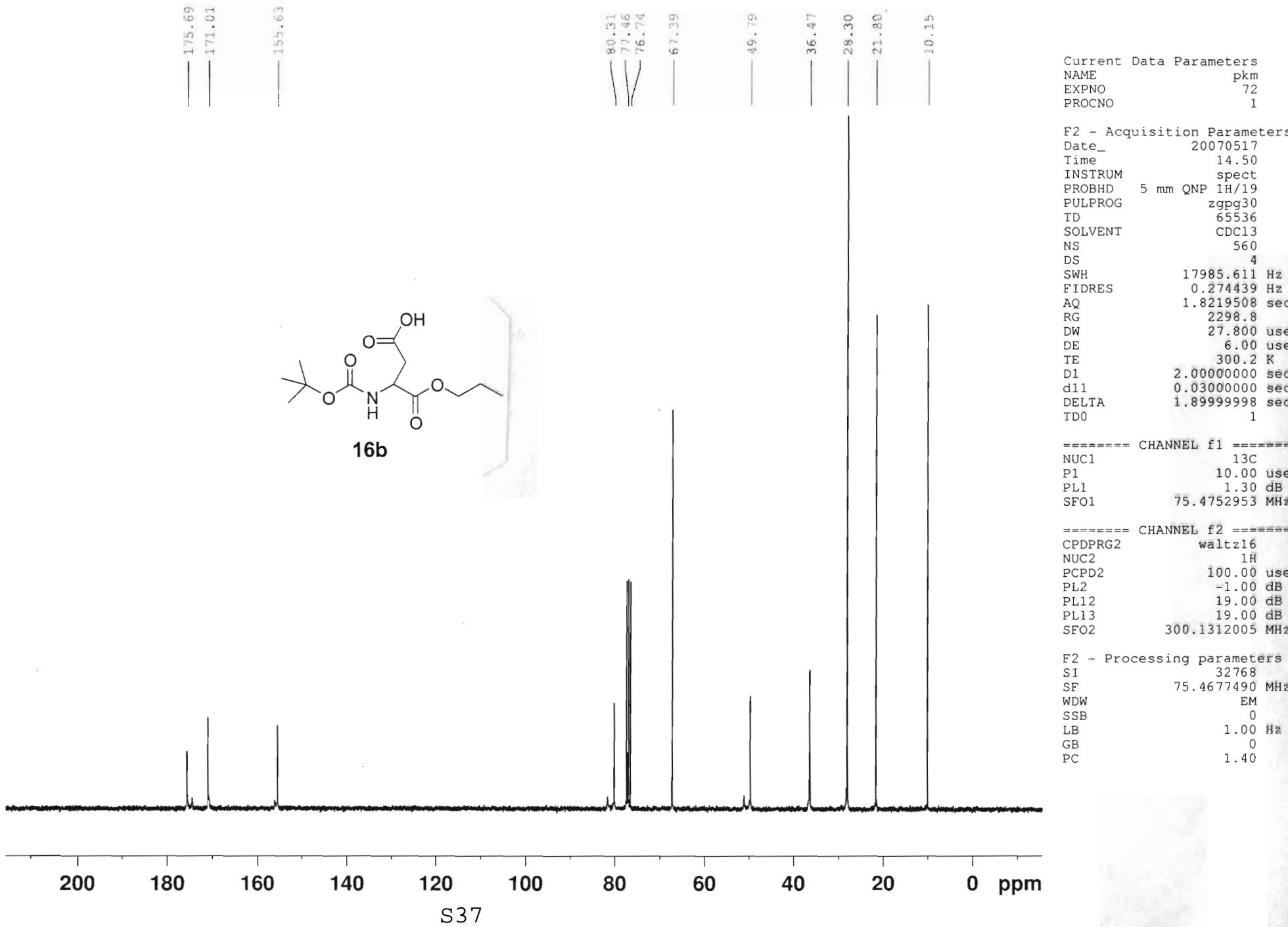


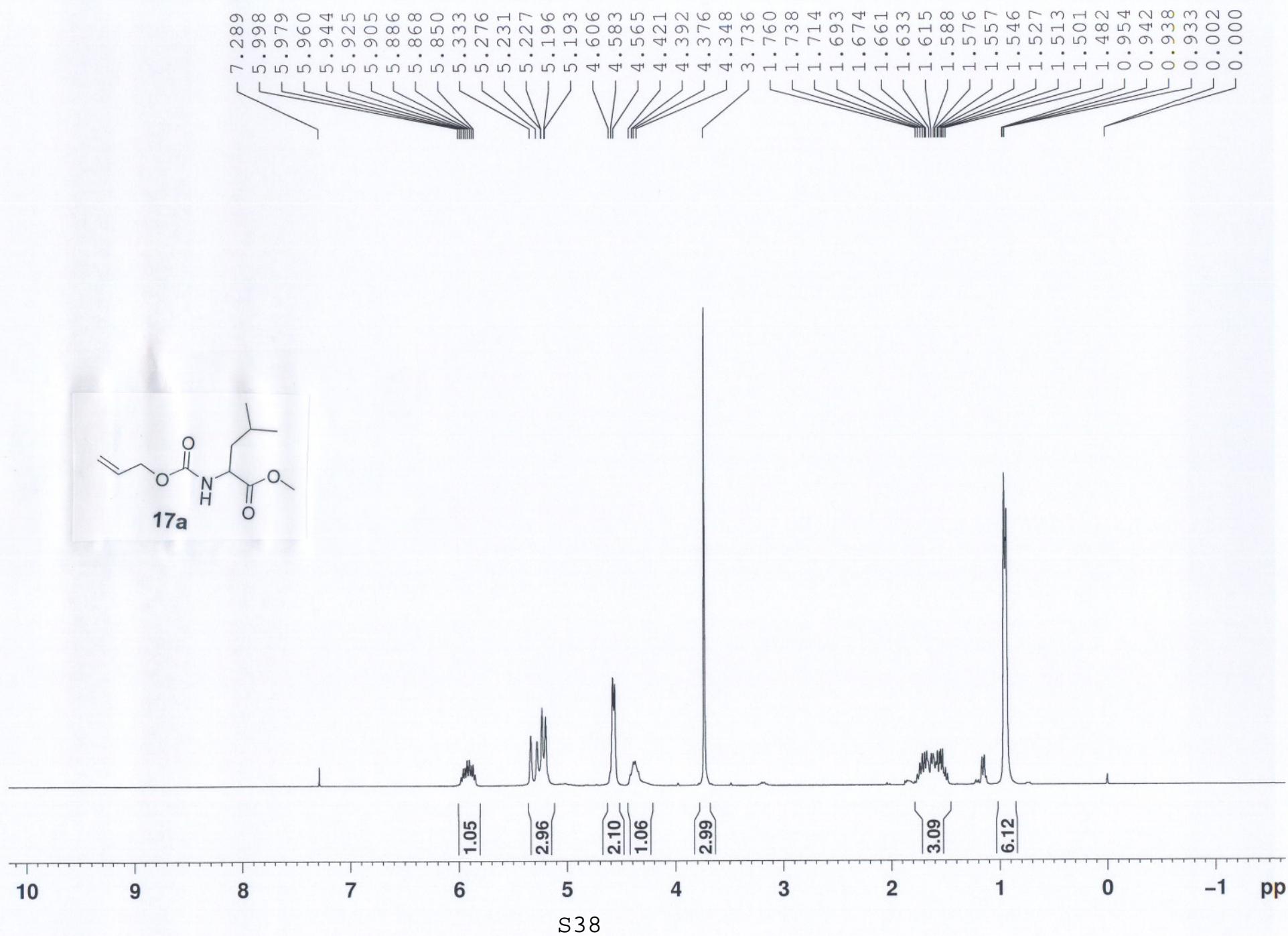


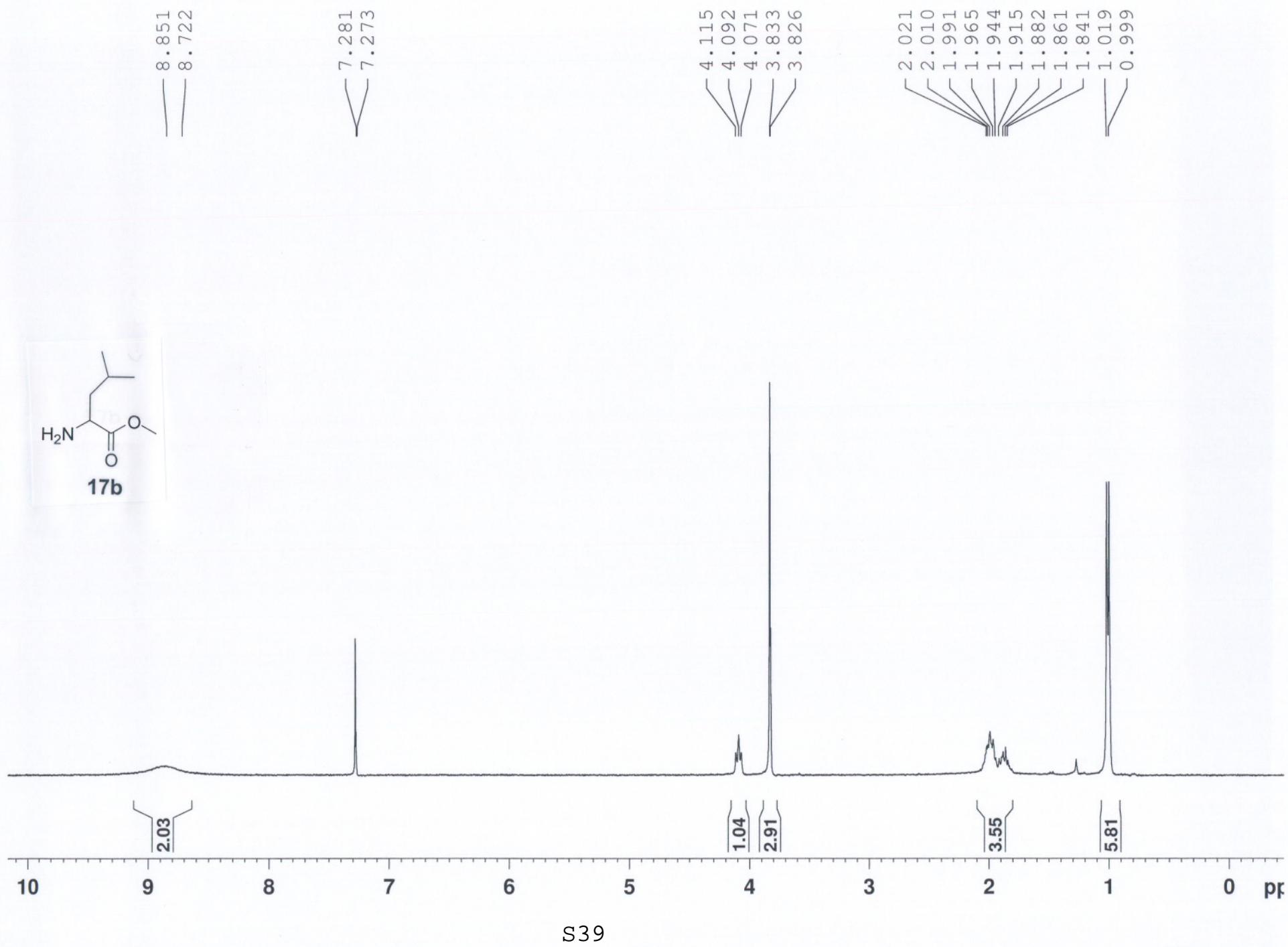


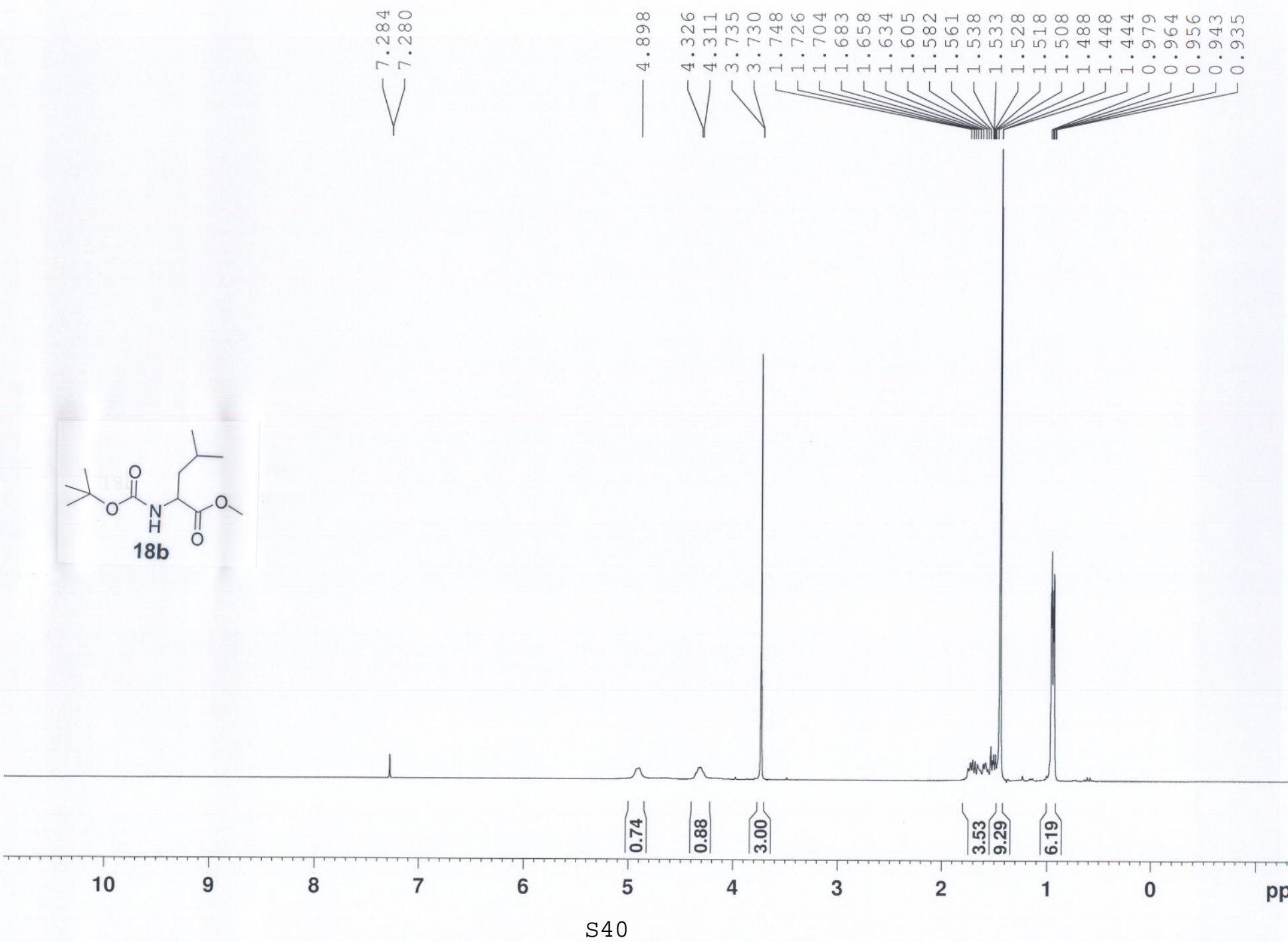
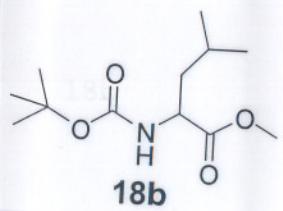


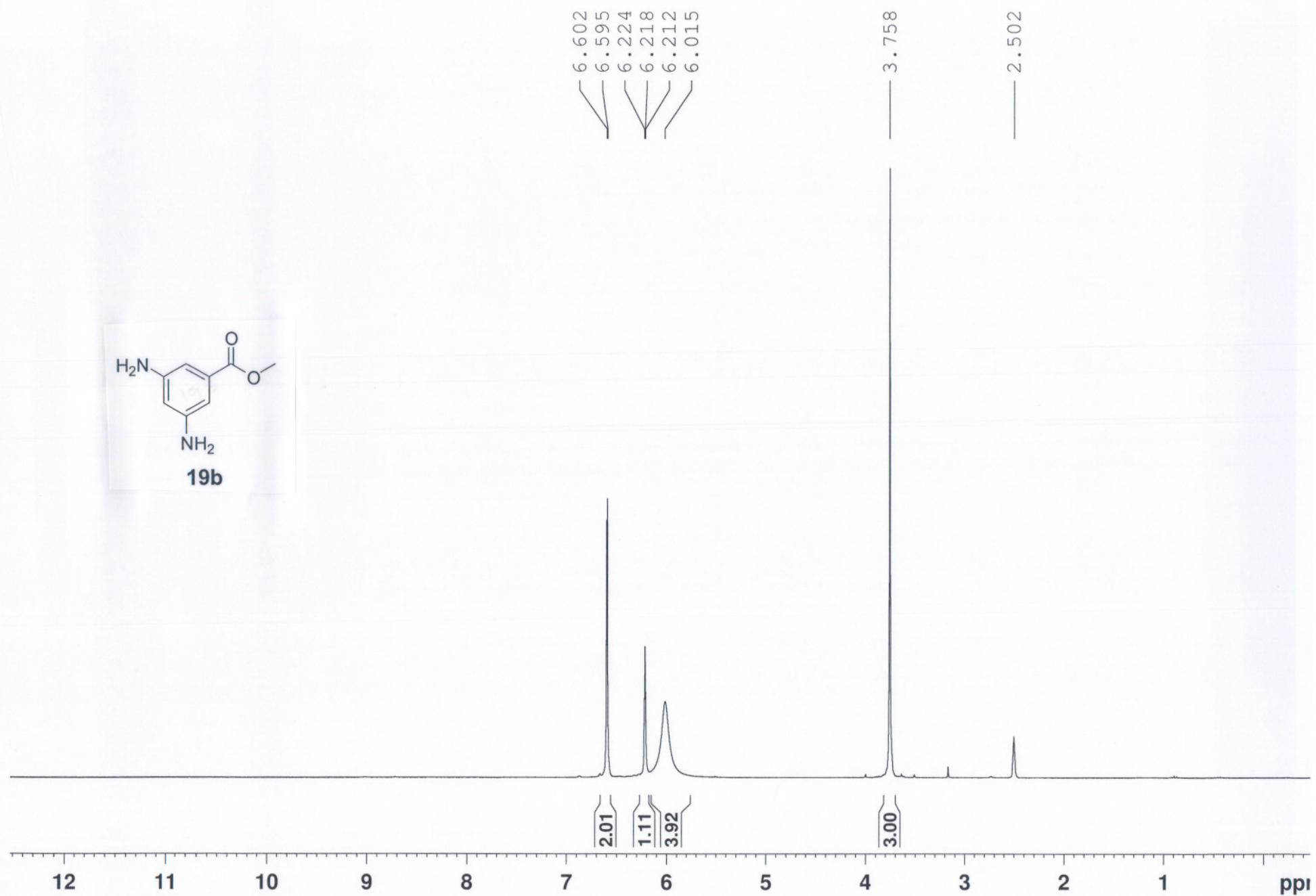
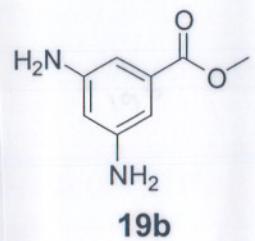


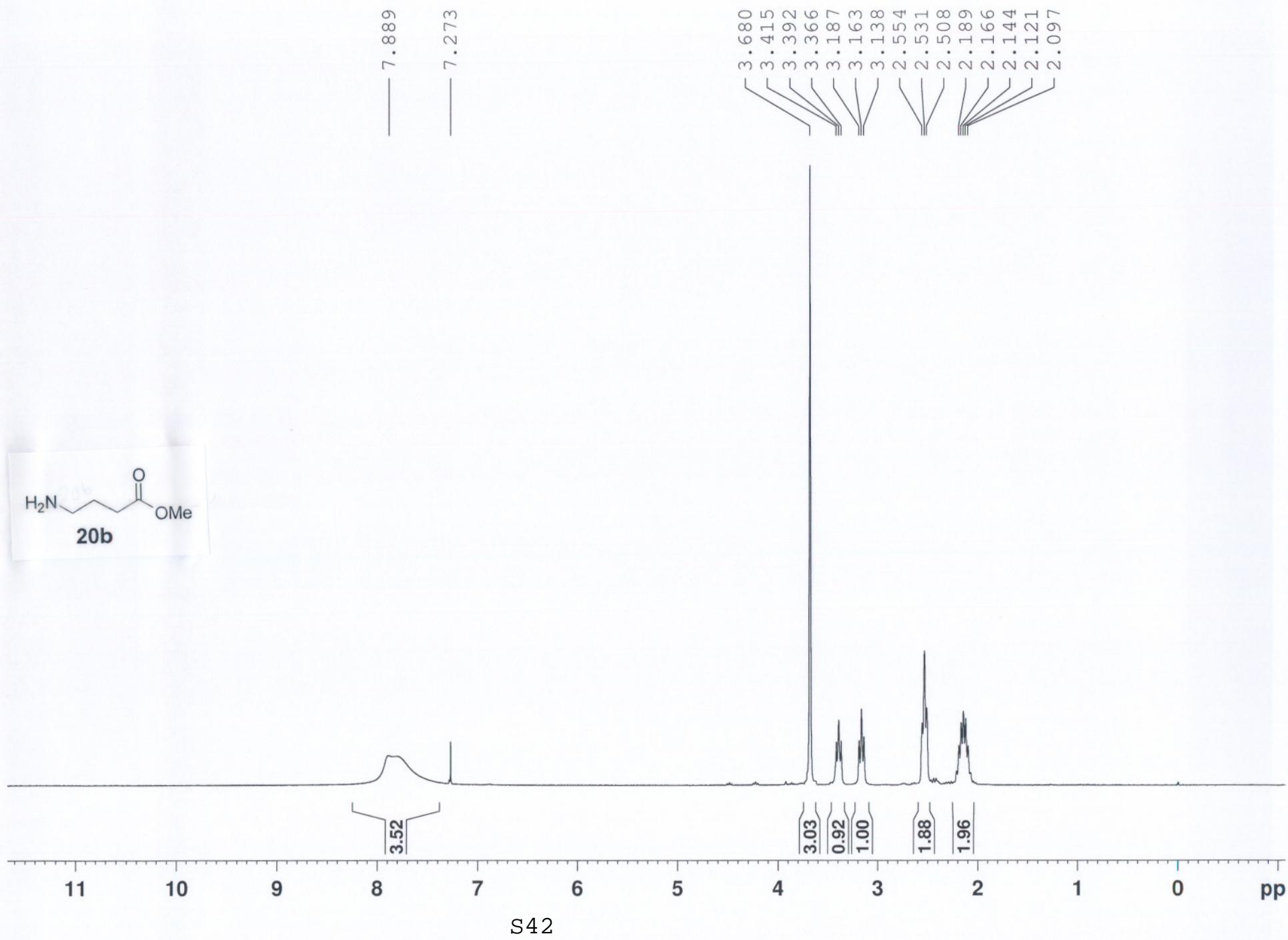
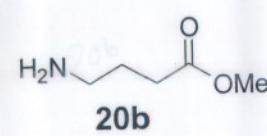












S42

